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A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment

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In this multicenter, open-label, randomized controlled trial, we determined whether 2-month prednisolone therapy for steroid-sensitive nephrotic syndrome was inferior or not to 6-month therapy despite significantly less steroid exposure. The primary end point was time from start of initial treatment to start of frequently relapsing nephrotic syndrome. The pre-specified non-inferiority margin was a hazard ratio of 1.3 with one-sided significance of 5%. We randomly assigned 255 children with an initial episode of steroid-sensitive nephrotic syndrome to either 2 - or 6-month treatment of which 246 were eligible for final analysis. The total prednisolone exposure counted both initial and relapse prednisolone treatment administered over 24 months. Median follow-up in months was 36.7 in the 2-month and 38.2 in the 6-month treatment group. Time to frequent relaps was similar in both groups; however, the median was reached only in the 6-month group (799 days). The hazard ratio was 0.86 (90% confidence interval, 0.64–1.16) and met the non-inferior margin. Time to first relapse was also similar in both groups: median day 242 (2-month) and 243 (6-month). Frequency and severity of adverse events were similar in both groups. Most adverse events were transient and occurred during initial or relapse therapy. Thus, 2 months of initial prednisolone therapy for steroid-sensitive nephrotic syndrome, despite less prednisolone exposure, is not inferior to 6 months of initial therapy in terms of time to onset of frequently relapsing nephrotic syndrome.

Idiopathic nephrotic syndrome (NS) is a disorder affecting the kidneys that is mainly characterized by high excretion of protein in the urine. Pediatric idiopathic NS is understood to be the most common cause of primary glomerular diseases, and it frequently occurs in infants aged 2–6 years. Most patients are presumed to have minor glomerular abnormality. Cellular immunologic abnormalities are believed to contribute to the condition, although its pathology remains unknown. In Europe and the United States, two in 100,000 children will develop idiopathic NS in a single year.[1] An 8-week corticosteroid regimen is the standard initial treatment for children with idiopathic NS, as outlined by the International Study of Kidney Disease in Children (ISKDC).[2,3] Although corticosteroids induce the remission of proteinuria in more than 80% of children with idiopathic NS, ~60% undergo proteinuria relapse. Previous research has shown that a high number of children undergo frequent relapse, and corticosteroid toxicities occur after repeated therapy.[2,3] Although some controlled studies[4–7] and a meta-analysis[8] show that long-term corticosteroid treatment up to 7 months maximum leads to a longer sustained remission of NS than ISKDC-recommended administration, the optimum

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[10]See appendix.

dose and duration of initial therapy are still unknown. A Cochrane review concluded that a well-designed and adequately powered randomized controlled trial is required to establish the optimum dose and duration of treatment.[8] The purpose of this study is to investigate whether 2 months of initial prednisolone therapy (ISKDC regimen) is not inferior to 6 months of initial therapy with an increasing cumulative dose, and to compare adverse events between treatment regimens.

RESULTS
Patient population
The study was conducted from September 6, 2007 until February 8, 2013. Figure 1 shows the trial profile. We assessed 255 patients from 90 hospitals (61 general, 7 children's, and 22 university hospitals) for eligibility. We randomly assigned 128 patients to the 2-month prednisolone group and 127 patients to the 6-month prednisolone group. We excluded nine patients from the analysis: six did not receive trial medication because of either early relapse after remission during the initial 4-week prednisolone treatment, or withdrawn consent, and three were excluded owing to a lack of participant data. Thus, we analyzed data for 246 patients. Median follow-up was 36.7 months in the 2-month group (interquartile range 27.8–46.4 months) and 38.2 months in the 6-month group (interquartile range 28.6–48.5 months). There was no difference in characteristics between the two groups (Table 1).

Primary end point
The primary end point was defined as the duration from start of initial treatment to diagnosis of frequently relapsing nephrotic syndrome (FRNS), or 'time to FRNS'. By the end of the 24-month intervention period, we observed 54 events in the 2-month group (comprising 46 FRNS [definition 1, 28; definition 2, 18], and 8 requiring immunosuppressant administration) and 58 events in the 6-month group

(comprising 45 FRNS [definition 1, 23; definition 2, 22], and 13 requiring immunosuppressant administration). Twenty-one patients required immunosuppressants owing to steroid-dependent or steroid-resistant relapse. Times to FRNS were similar in both groups: however, the median duration of time to FRNS was reached only in the 6-month group (at 799 days). The hazard ratio (HR) was 0.86 (90% confidence interval (CI), 0.64–1.16; Figure 2), and noninferiority of the 2-month group was confirmed significantly, with an HR margin of 1.3 ($P = 0.01$). Post-hoc analyses showed that age groups did not affect the median duration of time to FRNS. The HRs (95% CI) were 0.92 (0.59–1.45), 0.86 (0.41–1.84), and 0.74 (0.31–1.77) for the age groups 1–5 years, 6–10 years, and 11–15 years, respectively.

Secondary end points
Times to first relapse were similar in both groups: the median was 242 days and 243 days in the 2-month and 6-month treatment groups, respectively (HR = 0.97; 95% CI, 0.72–1.31; $P = 0.86$; Figure 3). The number of relapses per person-year during the trial intervention period was 1.25 times in the 2-month group and 1.33 times in the 6-month group, and the ratio was 0.94 (95% CI, 0.71–1.22; $P = 0.65$, Table 2). The median cumulative dose of prednisolone during the 2-year trial period in the 2-month group was also significantly lower than in the 6-month group (4621.9 [interquartile range = 2191.3–7472.5] vs. 6484.8 [interquartile range = 3701.0–9577.9], $P < 0.001$).

Adverse events
Frequency and severity of adverse events were similar in both groups (Table 3). Most adverse events were transient and occurred during initial therapy or relapse therapy. In our study, steroid dependency did not greatly affect the occurrence of adverse events. Two patients in the 2-month group had severe adverse events requiring hospitalization. One patient discontinued because of acute kidney failure during
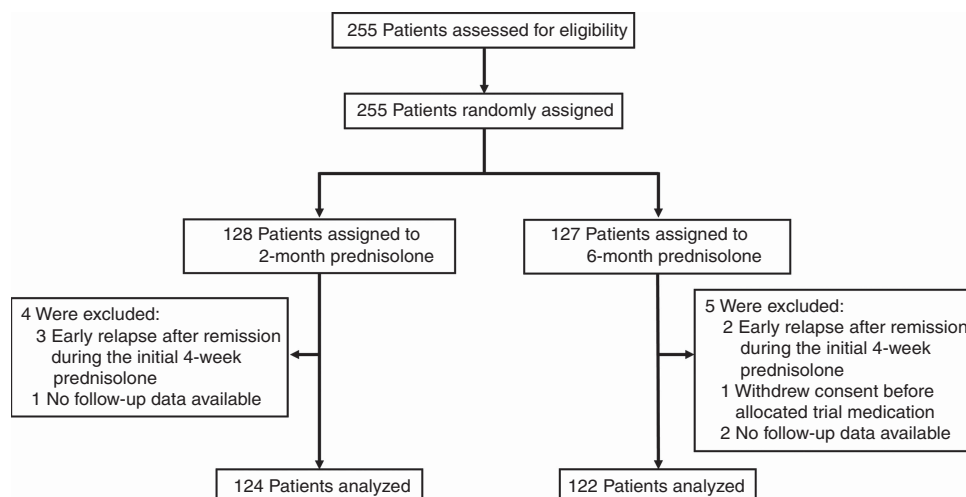

Figure 1 | Trial profile.

Table 1 | Baseline characteristics

	2-Month prednisolone (n = 124)	6-Month prednisolone (n = 122)	P-value
Male, n (%)	89 (71.8)	87 (71.3)	0.94
Age, mean (s.d.), years	6.7 (4.1)	6.3 (4.1)	0.42
Age group, years			
1–5, n (%)	67 (54.0)	66 (54.1)	0.99
6–10, n (%)	33 (26.6)	33 (27.1)	
11–15, n (%)	24 (19.4)	23 (18.9)	
Blood pressure, mean (s.d.), mm Hg			
Systolic	104.4 (10.7)	106.4 (12.0)	0.16
Diastolic	62.4 (10.0)	62.5 (11.3)	0.98
Serum albumin, mean (s.d.), g/l	1.4 (0.5)	1.4 (0.5)	0.90
Hospital, n (%)			
General	47 (65.3)	46 (64.8)	1.00
Children's	7 (9.7)	7 (9.9)	
University	18 (25.0)	18 (25.4)	
Quarterly distribution of disease onset, n (%)			
January–March	23 (18.7)	24 (19.7)	0.99
April–June	36 (29.3)	34 (27.9)	
July–September	30 (24.4)	31 (25.4)	
October–December	34 (27.6)	33 (27.0)	
Duration from the first episode to remission, mean (s.d.), days	9.7 (3.1)	10.0 (3.1)	0.45

Abbreviation: s.d., standard deviation.
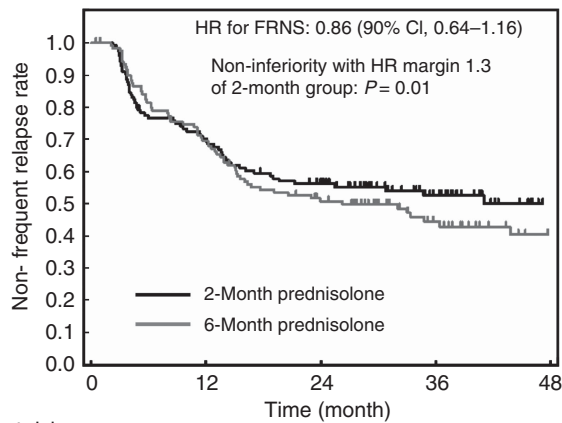
Figure 2 | Kaplan–Meier estimates of time to frequently relapsing nephrotic syndrome (FRNS). HR, hazard ratio.
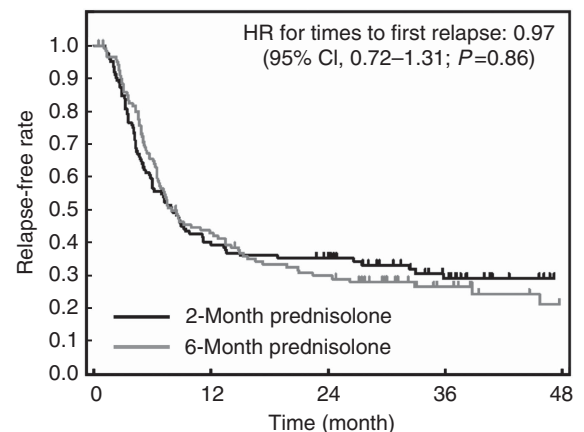
Figure 3 | Kaplan–Meier estimates of time to first relapse. HR, hazard ratio.

relapse (month 10) and recovered in 22 days. Another patient had pneumonia with influenza infection on the last date of the 2-month prednisolone treatment and recovered in 10 days. Height standard deviation scores show a significant decrease in growth at 2 months of follow-up compared with baseline ($P < 0.003$). In both groups, this was restored within 9 months after initial treatment commenced. Notably, one patient in the 6-month group was diagnosed with possible adrenal insufficiency owing to steroid withdrawal according to clinical symptoms (mild headache and mild nausea) when the patient switched to trial medication after the initial dose of prednisolone. Symptoms disappeared on the same day of onset without further treatment.

DISCUSSION

Extension of initial steroid treatment for more than 3 months to decrease the risk of relapse in children with steroid-sensitive (SS) NS has been widely described in previous studies.[4–10] However, 80–90% of children diagnosed with SSNS who are given new corticosteroid treatments continue to relapse, and ~50% relapse frequently.[11] Therefore, initial approaches to SSNS therapy are likely to be substantially

Table 2 | Number of relapses

	Total number of relapses	Duration of observation (person-year)	The number of relapses (per person-year)	Ratio of the number of relapses (CI)	*P*-value
2-Month prednisolone	301	240.93	1.25	0.94	0.65
6-Month prednisolone	309	232.62	1.33	(0.71–1.22)	

Abbreviation: CI, confidence interval.

Table 3 | Adverse events during the 24-month trial intervention period[a]

Event	2-Month prednisolone n = 124	6-Month prednisolone n = 122	*P*-value
Hypertension[b]	15	9	0.24
Cushingoid appearance			
Cushing (moon face)[b]	54	61	0.46
Central obesity[b]	20	34	0.052
Striae	1	0	1.00
Adrenal insufficiency	0	1	1.00
Ophthalmological abnormalities			
Glaucoma[b]	19	13	0.31
Cataract	0	0	
Severe infections			
Pneumonia[c]	1	0	1.00
Peptic ulcer	1	0	1.00
Acute kidney failure[c]	1	0	1.00
Hyperglycemia	2	3	0.64
Increased laboratory data			
AST[b]	14	11	0.58
ALT[b]	26	16	0.14
Amylase	3	0	1.00

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.
[a]Data are expressed as the number of events.
[b]Multiple reports were recorded for these adverse events.
[c]Severe adverse events requiring hospitalization.

different.[12] Our results demonstrate that extending initial steroid treatment, and even increasing the total dose of prednisolone (2240 vs. 3885 mg/m^2), does not improve clinical outcomes (time to FRNS, time to first relapse, the number of relapses, total prednisolone dose, and adverse events) for pediatric NS. Our results add to the Cochrane review by Hodgson *et al.*[8] by comparing treatment regimens of 2 vs. 6 months.

Our findings build on a 2013 study from the Netherlands. This well-designed, randomized, double-blind, placebo-controlled trial of children with NS clearly showed no improvement in clinical outcomes when the initial prednisolone treatment was extended from 3 to 6 months without an increasing cumulative dose.[13] However, despite the results of this trial, the most effective duration and dosage of prednisolone treatment for an initial episode of SSNS is still under debate.[14] Although our study has demonstrated that increasing the total dose in 2-month or 6-month regimens does not improve clinical outcomes, further investigation is

still required to determine the most effective duration and dosage regimen for initial SSNS.

A key strength of our trial is its unique design. This is a multicenter, randomized, controlled trial for noninferiority that compares the efficacy of the 2-month ISKDC regimen with a 6-month, long-term prednisolone regimen. The most important clinical objective of initial treatment of SSNS is to prevent frequent relapses. Consequently, the primary end point was set to time to FRNS rather than initial relapses.

Our data from several analyses consistently support noninferiority of the ISKDC regimen. In the current trial, a HR threshold of 1.3 for noninferiority of the primary end point is slightly high given the feasible study size. However, the posterior probability that a HR would be smaller than 1.1 and 1.2 (HRs that are commonly used as an upper equivalence margin) was 91 and 97%, respectively.

In our trial, noninferiority was found in FRNS (primary end point) and first relapse (secondary end point) between the ISKDC and 6-month regimens. This means that many patients relapse even while taking tapering-dose prednisolone (Figure 3). Previous studies vary in their observation of (frequent) relapses from either the start or end of initial therapy.[8,13] However, if analyses are performed from the end of initial therapy, relapses during tapering-dose prednisolone cannot be counted, possibly resulting in an inadequate interpretation. Therefore, we selected observations primarily from the start of initial therapy. In our study design, steroid-dependent NS was predicted to occur more frequently because of its definition in the 6-month regimen. This is one reason why we selected FRNS as a primary end point, and not steroid-dependent NS. In fact, time to steroid-dependent NS was significantly higher in the ISKDC regimen group (data not shown).

No significant difference in adverse events was observed between the two regimens in our large-scale trial, which is a similar finding to previous small-scale trials.[4–7] Most adverse events were transient and occurred during initial or relapse therapy. However, because the ISKDC regimen is generally less likely to cause adverse events owing to the lower dosage and the shorter duration, its use can be recommended.

A limitation of our trial is the open-label design, which may have introduced preconception bias. However, as our trial design is a noninferiority trial with regular visits, and relapses are measured objectively, we cannot assume positive placebo effects. Therefore, the open-label design of this study may have limited impact on preconception bias. Moreover, the results of this trial may partially be due to the relatively high rate of relapse compared with other studies.[5] The high

rate of relapse may be owing to our definition of relapse (proteinuria $2+$ or higher). It still remains unknown whether long prednisolone therapy consisting of a dose of $60 \, \text{mg/m}^2$ per day for 6 weeks, followed by alternate-day doses of $40 \, \text{mg/m}^2$ per 2 days for 6 weeks, is more effective against time to FRNS compared with the ISKDC regimen for treating idiopathic NS. In our study, only one patient withdrew consent. A low rate of consent withdrawal is common in Japan.[15,16] Cultural differences between countries may account for variations in rates of consent withdrawal.

In our study, steroid sensitivity was confirmed by day 21 in order to ensure time for eligibility screening. Generally, remission after 3 weeks is uncommon.[17] Therefore, as the effect of early confirmation of steroid sensitivity was slight, we decided to confirm steroid sensitivity by day 21.

We conducted a meta-analysis to address the differences between corticosteroid regimens in children with an initial episode of SSNS. We searched randomized controlled trials that compared durations of steroid therapy in children and reported the number of FRNS cases within 2 years (see the Supplementary Information online for a detailed search strategy). Meta-analysis of our study and five studies[6,13,18,19] showed a risk ratio (long vs short) of 0.99 (95% CI, 0.68–1.44, see Supplementary Figure 2A online), whereas meta-analysis of our study and the published studies only showed an risk ratio of 1.15 (95% CI: 0.95–1.40, Supplementary Figure 2B online). This result might indicate that long-term treatment is not superior but almost equivalent to ISKDC-standard therapy.

In conclusion, our study shows that extending initial prednisolone treatment from 2 to 6 months with an increasing dose does not improve clinical outcomes for pediatric NS. The original ISKDC regimen is not inferior to 6 months of initial therapy with an increasing cumulative dose. We assert that the ISKDC regimen is recommended as an initial treatment for pediatric idiopathic NS.

MATERIALS AND METHODS
Study design and patients
We conducted a multicenter, randomized, noninferiority, open-label trial at 90 hospitals in Japan and compared prednisolone treatment of 2 months (ISKDC regimen) with 6 months for children with a first episode of idiopathic NS. We diagnosed idiopathic NS and remission according to the ISKDC.[1] NS was defined as a urinary protein–creatinine ratio $\geqslant 1.8$ and albumin levels $\leqslant 25 \, \text{g/l}$ in serum. Remission was defined as a negative dipstick analysis for 3 consecutive days. Patients aged 1–15 years with a first episode of idiopathic NS were eligible if they had remission within 3 weeks of prednisolone administration. Patients were ineligible if they had secondary NS, renal insufficiency defined as creatinine clearance of $\leqslant 60 \, \text{ml/min}$ per $1.73 \, \text{m}^2$, active infections, poorly controlled hypertension, severe liver dysfunction, pregnancy, or a history of immunosuppressant administration.

Before enrollment, patients' guardians provided written informed consent, and informed assent was obtained from older children. This study was approved by the institutional review boards of participating hospitals, complied with the Declaration of Helsinki

and the Declaration of Istanbul, and adhered to the International Conference on Harmonisation Guidelines on Good Clinical Practice.

Randomization
Patients were randomly assigned to either the 2-month or 6-month group in a 1:1 ratio at the Japan Clinical Research Support Unit. We applied a minimization method using a computer-generated sequence (SAS PROC PLAN) with age (1–10 years or 11–15 years), sex, and institution as adjustment (stratification) factors. Patients, patients' guardians, treating physicians, and individuals assessing outcomes and analyzing data were not blinded to the patients' treatment assignments. Apart from the trial statistician and the data-monitoring committee, all treating physicians and other investigators remained blinded to the trial results until follow-up was completed.

Procedures
The first patient was randomized in September 2007, and the last patient in January 2011. Follow-up started at diagnosis and was truncated when the last enrolled patients finished the 24-month intervention.

All patients diagnosed with a first episode of idiopathic NS started initial therapy of $60 \, \text{mg/m}^2$ oral prednisolone in three divided doses (maximum of $80 \, \text{mg/day}$) daily for 4 weeks. Patients underwent a screening examination and were registered after their eligibility, including remission, was verified. Participants switched to trial medication after initial doses of prednisolone were given (Figure 4). If participants relapsed after remission during the initial 4-week prednisolone treatment, they were excluded.

Trial medication consisted of initial treatment regimens and relapse treatment, and was completed within a total of 24 months in both groups (Figures 4 and 5). The duration of long-term prednisolone treatment was set to 6 months, which is consistent with recommendations from a non-Japanese randomized controlled trial.[8] The cumulative dose of initial treatment was $2240 \, \text{mg/m}^2$ (2-month group) and $3885 \, \text{mg/m}^2$ (6-month group). Participants
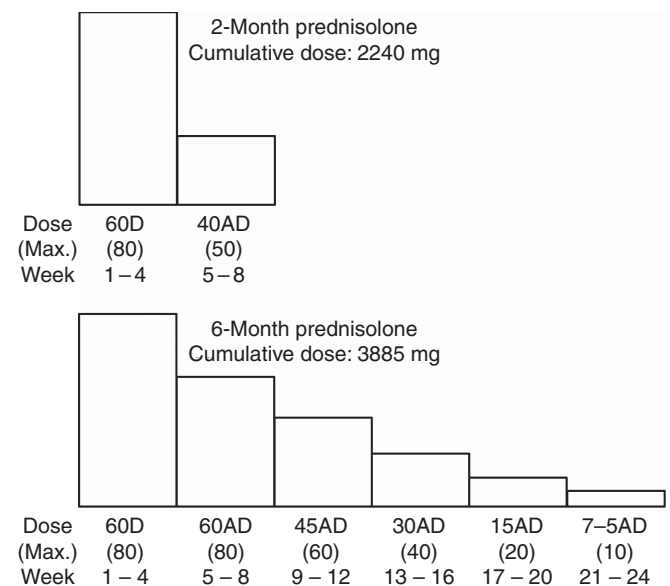

Figure 4 | Initial treatment regimens. Upper doses are in mg/m^2 per day. Maximum doses are in mg/day. D, daily; AD, alternate days.
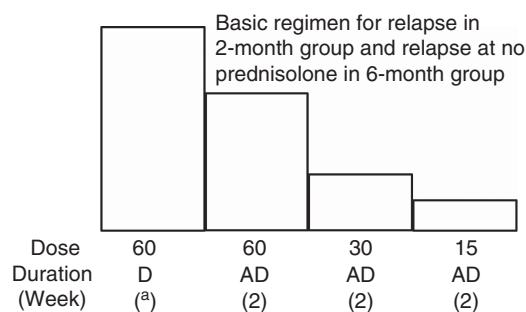
Figure 5 | Treatment regimens for relapse. [a]Until urinary protein is negative on 3 consecutive days using a urine dipstick test. Upper doses are in mg/m^2/day. A maximum dose of each is the same as initial treatments in Figure 4. AD, alternate days; D, daily.

who relapsed during the 24-month trial medication period received relapse treatment regimens (Figure 5). Relapse treatment was the same in both groups. However, relapse treatment given during the 6-month initial treatment was adjusted according to the initial treatment regimen in the 6-month group.

Participant characteristics (age, sex, physical characteristics, blood, and urine test results) were recorded at baseline. Clinical assessment and urine tests (urinalysis, qualitative and quantitative proteinuria, quantitative creatinine) were performed at 1, 2, 4, and 6 months after enrollment and every 3 months thereafter, and also on diagnosis of relapse. Blood analysis (complete blood cell count, blood chemistry) was performed at 1, 2, 6, and 12 months after enrollment, at the end of treatment, and at diagnosis of relapse only.

Adverse events were recorded throughout the trial period and assessed using Common Terminology Criteria for Adverse Events v3.0. Within 4 weeks of starting initial treatment, participants were screened for glaucoma by an ophthalmologist. Details about monitoring adverse events are described in the Supplementary Information online. Briefly, name of diagnosis, severity, seriousness, date of onset and disappearance, outcome, and assessment of causal relationship to the study drug were investigated at the start of study treatment and at 1, 2, 4, 6, 9, 12, 15, 18, 21, and 24 months after the start of study treatment (each within ± 2 weeks).

Outcomes

The primary end point was defined as the duration from start of initial treatment to diagnosis of FRNS, or 'time to FRNS'. Diagnosis of FRNS was based on the relapse dates according to the ISKDC. In our study, FRNS was defined as two relapses within 6 months of initial remission (definition 1), or four relapses within any 12-month period (definition 2), which included relapses during initial tapering treatment but excluded relapses with spontaneous remissions. Patients were observed for at least 2 years, on the basis of the Cochrane review, which states that the risk of relapse after 1–2 years was lower after long-term prednisolone treatment relative to the ISKDC regimen.[8] Relapse was defined as proteinuria 2 + or higher on dipstick analysis for 3 or more consecutive days or proteinuria 2 + or higher on dipstick analysis and serum albumin ⩽ 25 g/l. Immunosuppressant administration was prohibited in the protocol. However, if administration was undertaken for clinical necessity, e.g., steroid dependency, it was treated as an event in the primary analysis. Data for patients who did not experience these events were considered censored at the last examination. Important

secondary end points were time to first relapse, the number of relapses per person-year, total prednisolone dose, and adverse events.

Statistical analyses

The primary objective of this trial was to confirm noninferiority of initial therapy with 2-month treatment compared with 6-month treatment, with respect to time to FRNS. The noninferiority margin of HR for the 2-month to 6-month group was predefined to 1.3, and the significance level was set to 5% (one-sided). The former was determined based on surveys conducted among practicing pediatric nephrologists and other specialists before the protocol was developed.

On the basis of results from a previous study,[20] we assumed an event rate of 15 and 19% at 1 year in the 2- and 6-month groups, respectively. With a sample size of 125 patients in each treatment group, an HR test with a one-sided 5% significance level would have 70% power to confirm noninferiority. Accrual and follow-up times were specified to be 3 and 2 years, respectively.

As the previous study[20] was conducted more than 10 years earlier, it is possible that the current event rate of our study is lower than the previous study. We scheduled an interim analysis to take place just before the accrual completion date, which was performed in October 2010. A statistical test regarding the primary end point was not performed. The number of events observed matched that of the assumption, and the study plan was not changed.

Statistical analyses followed the protocol and the intention-to-treat principle. The Cox proportional hazard model was used to test noninferiority and estimate the HR with a 90% CI of the primary end point. The Kaplan–Meier method was used to summarize time to FRNS. These methods and the log-rank test were used to analyze time to first relapse. The number of relapses per person-year was calculated as the total number of relapses divided by the total observed person-years in each treatment group (Table 2). A permutation test was used to compare the number of relapses per person-year between groups. We compared the prednisolone total dose using the Wilcoxon test. The number of adverse events was compared using Poisson regression. For baseline characteristics, we compared distributions of continuous variables between groups using the *t*-test or Wilcoxon test, depending on the shape of the distribution. We analyzed categorical variables using the chi-squared test or Fisher's exact test. Posterior probability was calculated with the improper flat prior and the normal distribution to which log-HR was approximated. Except for noninferiority testing of the primary end point, we regarded a two-sided *P*-value < 0.05 to indicate statistical significance. We analyzed data using SAS software (version 9.3) and calculated the sample size using the SAS POWER procedure.

SUPPLEMENTARY MATERIAL
Figure S2. (A) Meta-analysis of studies comparing 2–3 months of prednisolone to 5–6 months of prednisolone for children with their first episode of nephrotic syndrome, with an outcome showing the number of children with frequent relapses after 1–2 years. (B) Sensitivity analysis excluding Sharma 2002 (unpublished conference proceeding) from Fig. A.
Supplementary material is linked to the online version of the paper at http://www.nature.com/ki

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APPENDIX
Japanese Study Group of Kidney Disease in Children (JSKDC). JSKDC has been supported by grants from the Ministry of Health, Labour and Welfare, Japan. Members of the JSKDC are as follows.

Steering Committee: Norishige Yoshikawa (chair), Kazumoto Iijima, Hidefumi Nakamura, Masataka Honda, and Mayumi Sako.

JSKDC study office: Koichi Nakanishi (chair) and Yuko Shima.

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