Clinical trial results:
Long-term tapering versus standard prednisolone (steroid) therapy for the treatment of the initial episode of childhood nephrotic syndrome: national multicentre randomised double blind trial

Summary

EudraCT number	2010-022489-29
Trial protocol	GB
Global end of trial date	07 April 2017

Results information

Result version number	v1 (current)
This version publication date	17 May 2018
First version publication date	17 May 2018
Summary attachment (see zip file)	PREDNOS End of Study Report (PREDNOS End of Study report signed 280218.pdf)

Trial information

Trial identification

Sponsor protocol code	RG_08-015

Additional study identifiers

ISRCTN number	ISRCTN16645249
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS Project Code: 59508, CTA number: 21761/0255/001-0001, NIHR CRN Study ID: 9617, REC Reference number: 10/H1008/122, HTA Grant Ref.: 08/53/31

Notes:

Sponsors

Sponsor organisation name	University of Birmingham
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Sponsor organisation address	29 Grafton Street, Manchester, United Kingdom, M13 9WU
Public contact	Professor Nicholas JA Webb, Manchester University NHS Foundation Trust, +44 161 701 2961, Nicholas.Webb@mft.nhs.uk
Scientific contact	Professor Nicholas JA Webb, Manchester University NHS Foundation Trust, +44 161 701 2961, Nicholas.Webb@mft.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 October 2016
Global end of trial reached?	Yes
Global end of trial date	07 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether an extended 16 week course of prednisolone increases the time to first relapse in children presenting with steroid sensitive nephrotic syndrome compared with the standard 8 week course.

Protection of trial subjects:

The trial was designed to match standard clinical practice as much as possible and so cause no more pain and distress to that that would be experienced (if at all) in standard clinical practice.
The study protocol included the collection of a single 10ml EDTA blood sample for a genetic sub-study (not funded as part of the National Institute for Health Research (NIHR) award). This was obtained at the time of routine venous sampling for clinical purposes wherever possible, however the ethical approval did allow a stand-alone blood test to be collected solely for the purposes of the research project. Any potential discomfort associated with blood sampling was minimised by the use of clinical staff that were experienced in paediatric venepuncture and the use of both distraction therapy and topical anaesthetic agents as is routine clinical practice. The small volume of blood collected on one single occasion was not deemed sufficient to cause hypovolaemia or anaemia in participants of one to 14 years of age.
Prednisolone was supplied as 5mg tablets alongside matching placebo, so that participants in both treatment groups received the same number of tablets at any time-point in the study. Participants who were unable to swallow tablets whole were allowed to crush study drug using a tablet crusher, which was supplied upon request.

Background therapy:

None

Evidence for comparator:

The extended course (sixteen week) tapering prednisolone regimen was compared with the standard eight week regimen as originally proposed by the International Study of Kidney Disease in Children (ISKDC).
The first standardised corticosteroid treatment regimen was introduced by the ISKDC in the 1960s and consisted of prednisone 60mg/m2 (maximum 80mg) given daily for 4 weeks followed by 40mg/m2 (maximum 60mg) on 3 consecutive days out of seven for a total of 4 weeks. Many centres made a minor modification whereby 40mg/m2 was given on alternate days during the second four-week period, a regimen which is still in widespread use (“standard regimen”).

Actual start date of recruitment	02 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 237
Worldwide total number of subjects	237
EEA total number of subjects	237

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	17
Children (2-11 years)	209
Adolescents (12-17 years)	11
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

124 district general hospitals and tertiary regional paediatric nephrology centres throughout the UK took part in the study. PREDNOS opened to recruitment in July 2011. The first participant was recruited into the trial 2nd August 2011. 237 participants were recruited to the study in total, the last entering the study on 7th October 2014.

Pre-assignment

Screening details:

Formal screening logs were requested, in keeping with other studies these were not kept well, however, based on known epidemiological data, we estimate that we have managed to include 34% of newly presenting patients over a 3 year and 2 month recruitment period. Indicating a high level of acceptability of the trial among families and clinicians.

Pre-assignment period milestones

Number of subjects started	237
Number of subjects completed	223

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Development of corticosteroid resistance: 14

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

All those involved in treating the participant, the participant and their parents/guardians were masked as to the randomised treatment allocation. Once the participant had been randomised, the central pharmacy at the Birmingham Children's Hospital dispensed the PREDNOS trial medication by post to the participants home. Only delegated staff at pharmacy could view the treatment allocation, via a secure login, to assemble the study drug treatment blister packs and dispatch these.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard course

Arm description:

Standard course (SC) prednisolone therapy (the ISKDC regimen: prednisolone 60mg/m2/day (maximum dose 80mg) for four weeks followed by 40mg/m2 (maximum dose 60mg) on alternate days for a further four weeks).

Arm type	Active comparator
Investigational medicinal product name	PREDNISOLONE
Investigational medicinal product code	ATC CODE: H02A B06
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisolone 60mg/m2/day (maximum dose 80mg) for four weeks followed by 40mg/m2 (maximum dose 60mg) on alternate days for a further four weeks

Arm title	Extended course

Arm description:

Extended course (EC) prednisolone therapy (prednisolone 60mg/m2/day (maximum 80mg) for four weeks followed by 60mg/m2 (maximum 60mg) on alternate days for two weeks with a subsequent gradual reduction in dose over a total of 12 weeks (tapering by 10mg/m2 every two weeks), resulting in a total course of prednisolone of 16 weeks

Arm type	Experimental
Investigational medicinal product name	PREDNISOLONE
Investigational medicinal product code	ATC CODE: H02A B06
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisolone 60mg/m2/day (maximum dose 80mg) for four weeks followed by 60mg/m2 (maximum 60mg) on alternate days for two weeks with a subsequent gradual reduction in dose over a total of 12 weeks (tapering by 10mg/m2 every two weeks), resulting in a total course of prednisolone of 16 weeks

Number of subjects in period 1[1]	Standard course	Extended course
Started	109	114
Completed	101	106
Not completed	8	8
Consent withdrawn by subject	7	5
Physician decision	-	1
Compliance issue	1	-
Lost to follow-up	-	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 237 patients (worldwide number) were enrolled into the PREDNOS study. 14 participants (9 in the SC group and 5 in the EC group) who had initially responded to open label prednisolone suggesting that they were corticosteroid sensitive developed proteinuria. These patients were deemed to be corticosteroid resistant and and were withdrawn from the study as per protocol.

Baseline characteristics

Reporting groups	
Reporting group title	Standard course
Reporting group description:	
Standard course (SC) prednisolone therapy (the ISKDC regimen: prednisolone 60mg/m2/day (maximum dose 80mg) for four weeks followed by 40mg/m2 (maximum dose 60mg) on alternate days for a further four weeks).	
Reporting group title	Extended course
Reporting group description:	
Extended course (EC) prednisolone therapy (prednisolone 60mg/m2/day (maximum 80mg) for four weeks followed by 60mg/m2 (maximum 60mg) on alternate days for two weeks with a subsequent gradual reduction in dose over a total of 12 weeks (tapering by 10mg/m2 every two weeks), resulting in a total course of prednisolone of 16 weeks	

Reporting group values	Standard course	Extended course	Total
Number of subjects	109	114	223
Age categorical			
Data reported on ITT analysis population (n=223)			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	29	28	57
Children (2-11 years)	77	80	157
Adolescents (12-17 years)	3	6	9
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous			
Data reported on ITT analysis population (n=223)			
Units: years			
arithmetic mean	4.7	5.1	
standard deviation	± 2.9	± 3.2	-
Gender categorical			
Units: Subjects			
Female	31	46	77
Male	78	68	146
Ethnicity			
Data reported on ITT analysis population (n=223)			
Units: Subjects			
South Asian	21	23	44
White	73	75	148
Other / Not stated	15	16	31
BMI Percentile			
Data reported on ITT analysis population (n=223)			
Units: Subjects			
Underweight	2	0	2
Healthy	52	48	100

Overweight	19	24	43
Obese	36	42	78

Open label prednisolone dose			
Data reported on ITT analysis population (n=223)			
Units: mg/m2/day			
arithmetic mean	58.5	58.0	
standard deviation	± 5.9	± 6.8	-

Subject analysis sets

Subject analysis set title	ITT population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Two hundred and thirty-seven participants were recruited into the study from 86 UK centres between 2nd August 2011 and 7th October 2014; 118 were randomised to SC and 119 to EC therapy. Fourteen participants (SC: 9 vs. EC: 5) were withdrawn during the first few weeks of the trial (following randomisation) as per the protocol due to the development of corticosteroid resistance following an initial response to open-label prednisolone therapy, leaving a modified ITT population of 223 participants.

Reporting group values	ITT population		
Number of subjects	223		
Age categorical			
Data reported on ITT analysis population (n=223)			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	57		
Children (2-11 years)	157		
Adolescents (12-17 years)	9		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Data reported on ITT analysis population (n=223)			
Units: years			
arithmetic mean	4.9		
standard deviation	± 3.1		
Gender categorical			
Units: Subjects			
Female	77		
Male	146		
Ethnicity			
Data reported on ITT analysis population (n=223)			
Units: Subjects			
South Asian	44		
White	148		
Other / Not stated	31		
BMI Percentile			

Data reported on ITT analysis population (n=223)			
Units: Subjects			
Underweight	2		
Healthy	100		
Overweight	43		
Obese	78		
Open label prednisolone dose			
Data reported on ITT analysis population (n=223)			
Units: mg/m2/day			
arithmetic mean	58.2		
standard deviation	± 6.4		

End points

End points reporting groups

Reporting group title	Standard course

Reporting group description:

Standard course (SC) prednisolone therapy (the ISKDC regimen: prednisolone 60mg/m2/day (maximum dose 80mg) for four weeks followed by 40mg/m2 (maximum dose 60mg) on alternate days for a further four weeks).

Reporting group title	Extended course

Reporting group description:

Extended course (EC) prednisolone therapy (prednisolone 60mg/m2/day (maximum 80mg) for four weeks followed by 60mg/m2 (maximum 60mg) on alternate days for two weeks with a subsequent gradual reduction in dose over a total of 12 weeks (tapering by 10mg/m2 every two weeks), resulting in a total course of prednisolone of 16 weeks

Subject analysis set title	ITT population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Two hundred and thirty-seven participants were recruited into the study from 86 UK centres between 2nd August 2011 and 7th October 2014; 118 were randomised to SC and 119 to EC therapy. Fourteen participants (SC: 9 vs. EC: 5) were withdrawn during the first few weeks of the trial (following randomisation) as per the protocol due to the development of corticosteroid resistance following an initial response to open-label prednisolone therapy, leaving a modified ITT population of 223 participants.

Primary: Time to first relapse

End point title	Time to first relapse

End point description:

To avoid the potential for bias, if a participant relapsed before 18 weeks, their relapse time was set to 18 weeks. Participants in the EC group received corticosteroids up to week 16, so this also accounts for any possible difference between the groups in corticosteroid dependency. A secondary analysis was performed which analysed time to first relapse using the actual relapse date.

End point type	Primary

End point timeframe:

Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months.

End point values	Standard course	Extended course		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: Relapse	88	91		

Attachments (see zip file)	PREDNOS Figure Time to First Relapse/PREDNOS Figure Time

Statistical analyses

Statistical analysis title	Time to first relapse

Statistical analysis description:

Hazard ratio from Cox proportional hazards model. P-value from log-rank test.

Comparison groups	Standard course v Extended course

Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.17

Secondary: Number of relapses

End point title	Number of relapses

End point description:

Participants were followed-up with visits at 4, 8, 12 and 16 weeks, and then at 5, 6, 8, 10, 12, 18, 24, 30, 36, 42 and 48 months after commencing open-label prednisolone. Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months; the study completed when the last participant had completed 24 months of follow-up. Number of relapses reported during the trial.

End point type	Secondary

End point timeframe:

Participants were followed-up for a minimum of 24 months and up to a maximum of 48

End point values	Standard course	Extended course		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: Number of Relapses	394	454		

Attachments (see zip file)	PREDNOS Figure Secondary Outcome Measures/PREDNOS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who developed FRNS

End point title	Number of participants who developed FRNS

End point description:

Participants were followed-up with visits at 4, 8, 12 and 16 weeks, and then at 5, 6, 8, 10, 12, 18, 24, 30, 36, 42 and 48 months after commencing open-label prednisolone. Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months; the study completed when the last participant had completed 24 months of follow-up.
FRNS defined as 2 relapses or more in the first 6 months following presentation or 4 relapses within any 12 month period.

End point type	Secondary

End point timeframe:

Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months

End point values	Standard course	Extended course		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: Number of Participants	55	60		

Statistical analyses

Statistical analysis title	Number of participants who developed FRNS
Comparison groups	Standard course v Extended course
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.35

Secondary: Number of participants who developed SDNS

End point title	Number of participants who developed SDNS

End point description:

Participants were followed-up with visits at 4, 8, 12 and 16 weeks, and then at 5, 6, 8, 10, 12, 18, 24, 30, 36, 42 and 48 months after commencing open-label prednisolone. Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months; the study completed when the last participant had completed 24 months of follow-up.
SDNS defined as participants who relapse on or within 14 days of completing steroid therapy.

End point type	Secondary

End point timeframe:

Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months

End point values	Standard course	Extended course		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: Number of Participants	48	48		

Statistical analyses

Statistical analysis title	Number of participants who developed SDNS
Comparison groups	Extended course v Standard course
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.29

Secondary: Mean number of relapses per participant

End point title	Mean number of relapses per participant

End point description:

Participants were followed-up with visits at 4, 8, 12 and 16 weeks, and then at 5, 6, 8, 10, 12, 18, 24, 30, 36, 42 and 48 months after commencing open-label prednisolone. Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months; the study completed when the last participant had completed 24 months of follow-up.

End point type	Secondary

End point timeframe:

Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months

End point values	Standard course	Extended course		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: Mean number of relapses				
arithmetic mean (standard deviation)	3.61 (± 3.25)	3.98 (± 3.30)		

Statistical analyses

Statistical analysis title	Mean number of relapses per participant
Comparison groups	Standard course v Extended course
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	t-test, 2-sided
Parameter estimate	Incident Rate Ratio
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.39

Secondary: Number of participants who received second line immunosuppressants	
End point title	Number of participants who received second line immunosuppressants
End point description:	
Participants were followed-up with visits at 4, 8, 12 and 16 weeks, and then at 5, 6, 8, 10, 12, 18, 24, 30, 36, 42 and 48 months after commencing open-label prednisolone. Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months; the study completed when the last participant had completed 24 months of follow-up.	
End point type	Secondary
End point timeframe:	
Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months	

End point values	Standard course	Extended course		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	114		
Units: Number of Participants	61	62		

Statistical analyses

Statistical analysis title	No. of participants who received 2nd line immunosu
Comparison groups	Standard course v Extended course
Number of subjects included in analysis	223
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	Chi-squared
Parameter estimate	Risk ratio (RR)
Point estimate	0.97

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.23

Secondary: Mean total prednisolone dose (mg)

End point title	Mean total prednisolone dose (mg)

End point description:

Participants were followed-up with visits at 4, 8, 12 and 16 weeks, and then at 5, 6, 8, 10, 12, 18, 24, 30, 36, 42 and 48 months after commencing open-label prednisolone. Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months; the study completed when the last participant had completed 24 months of follow-up.

End point type	Secondary

End point timeframe:

Participants were followed-up for a minimum of 24 months and up to a maximum of 48 months

End point values	Standard course	Extended course		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	94		
Units: mg				
arithmetic mean (standard deviation)	5474.6 (± 3697.3)	6674.1 (± 4998.2)		

Statistical analyses

Statistical analysis title	Mean total prednisolone dose (mg)

Statistical analysis description:

Total dose of prednisolone received during the study (following completion of study medication).

Comparison groups	Standard course v Extended course
Number of subjects included in analysis	184
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.07
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1199.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-83.8
upper limit	2482.8

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE occurring during trial treatment or up to 3 months following trial treatment

Adverse event reporting additional description:

Only targeted non-serious adverse events were collected: Data reported on cataract at 12 and 24 months, poor behaviour, abdominal pain, glycosuria, striae, hypertrichosis, acne, Cushingoid facies and increased appetite at Week 16, 6 months, 12 months and 24 months.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Standard Course Therapy

Reporting group description:

Two hundred and thirty-seven participants were recruited into the study from 86 UK centres between 2nd August 2011 and 7th October 2014; 118 were randomised to SC and 119 to EC therapy. Fourteen participants (SC: 9 vs. EC: 5) were withdrawn during the first few weeks of the trial (following randomisation) as per the protocol due to the development of corticosteroid resistance following an initial response to open-label prednisolone therapy, leaving an ITT population of 223 participants (SC: 109 vs EC: 114).

Reporting group title	Extended Course Therapy

Reporting group description:

Two hundred and thirty-seven participants were recruited into the study from 86 UK centres between 2nd August 2011 and 7th October 2014; 118 were randomised to SC and 119 to EC therapy. Fourteen participants (SC: 9 vs. EC: 5) were withdrawn during the first few weeks of the trial (following randomisation) as per the protocol due to the development of corticosteroid resistance following an initial response to open-label prednisolone therapy, leaving an ITT population of 223 participants (SC: 109 vs EC: 114).

Serious adverse events	Standard Course Therapy	Extended Course Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	27 / 109 (24.77%)	19 / 114 (16.67%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 109 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Afebrile seizure			

subjects affected / exposed	0 / 109 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Death			
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Relapse of nephrotic syndrome			
subjects affected / exposed	14 / 109 (12.84%)	14 / 114 (12.28%)	
occurrences causally related to treatment / all	0 / 19	2 / 19	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal biopsy			
subjects affected / exposed	3 / 109 (2.75%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute renal failure			
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Soft tissue injury			
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	0 / 109 (0.00%)	1 / 114 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	8 / 109 (7.34%)	5 / 114 (4.39%)	
occurrences causally related to treatment / all	3 / 10	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Standard Course Therapy	Extended Course Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 109 (100.00%)	112 / 114 (98.25%)	
General disorders and administration site conditions			
Week 16 Poor Behaviour	Additional description: Poor behaviour at 16 weeks		
subjects affected / exposed	98 / 109 (89.91%)	86 / 114 (75.44%)	
occurrences (all)	98	86	
Month 6 Poor Behaviour	Additional description: Poor behaviour at 6 months		
subjects affected / exposed	99 / 109 (90.83%)	92 / 114 (80.70%)	
occurrences (all)	99	92	
Month 12 Poor Behaviour	Additional description: Poor behaviour at 12 months		
subjects affected / exposed	100 / 109 (91.74%)	93 / 114 (81.58%)	
occurrences (all)	100	93	
Month 24 Poor Behaviour	Additional description: Poor behaviour at 24 months		
subjects affected / exposed	101 / 109 (92.66%)	94 / 114 (82.46%)	
occurrences (all)	101	94	
Eye disorders			

Month 12 Cataract	Additional description: Cataract at 12 months		
subjects affected / exposed	1 / 109 (0.92%)	0 / 114 (0.00%)	
occurrences (all)	1	0	
Month 24 Cataract	Additional description: Cataract at 24 months		
subjects affected / exposed	1 / 109 (0.92%)	1 / 114 (0.88%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Week 16 Abdominal Pain	Additional description: Abdominal pain at 16 weeks		
subjects affected / exposed	31 / 109 (28.44%)	28 / 114 (24.56%)	
occurrences (all)	31	28	
Month 6 Abdominal Pain	Additional description: Abdominal pain at 6 months		
subjects affected / exposed	35 / 109 (32.11%)	38 / 114 (33.33%)	
occurrences (all)	35	38	
Month 12 Abdominal Pain	Additional description: Abdominal pain at 12 months		
subjects affected / exposed	46 / 109 (42.20%)	44 / 114 (38.60%)	
occurrences (all)	46	44	
Month 24 Abdominal Pain	Additional description: Abdominal pain at 24 months		
subjects affected / exposed	51 / 109 (46.79%)	49 / 114 (42.98%)	
occurrences (all)	51	49	
Skin and subcutaneous tissue disorders			
Week 16 Striae	Additional description: Striae assessed at Week 16		
subjects affected / exposed	3 / 109 (2.75%)	8 / 114 (7.02%)	
occurrences (all)	3	8	
Month 6 Striae	Additional description: Striae assessed at 6 months		
subjects affected / exposed	4 / 109 (3.67%)	11 / 114 (9.65%)	
occurrences (all)	4	11	
Month 12 Striae	Additional description: Striae assessed at 12 months		
subjects affected / exposed	6 / 109 (5.50%)	11 / 114 (9.65%)	
occurrences (all)	6	11	
Month 24 Striae	Additional description: Striae assessed at 24 months		
subjects affected / exposed	7 / 109 (6.42%)	14 / 114 (12.28%)	
occurrences (all)	7	14	
Week 16 Hypertrichosis	Additional description: Hypertrichosis assessed at Week 16		
subjects affected / exposed	25 / 109 (22.94%)	34 / 114 (29.82%)	
occurrences (all)	25	34	
Month 6 Hypertrichosis	Additional description: Hypertrichosis assessed at 6 months		

subjects affected / exposed	30 / 109 (27.52%)	40 / 114 (35.09%)	
occurrences (all)	30	40	
Month 12 Hypertrichosis	Additional description: Hypertrichosis assessed at 12 months		
subjects affected / exposed	37 / 109 (33.94%)	42 / 114 (36.84%)	
occurrences (all)	37	42	
Month 24 Hypertrichosis	Additional description: Hypertrichosis assessed at 24 months		
subjects affected / exposed	41 / 109 (37.61%)	45 / 114 (39.47%)	
occurrences (all)	41	45	
Week 16 Acne	Additional description: Acne at Week 16		
subjects affected / exposed	3 / 109 (2.75%)	6 / 114 (5.26%)	
occurrences (all)	3	6	
Month 6 Acne	Additional description: Acne at 6 months		
subjects affected / exposed	6 / 109 (5.50%)	9 / 114 (7.89%)	
occurrences (all)	6	9	
Month 12 Acne	Additional description: Acne at 12 months		
subjects affected / exposed	7 / 109 (6.42%)	11 / 114 (9.65%)	
occurrences (all)	7	11	
Month 24 Acne	Additional description: Acne at 24 months		
subjects affected / exposed	7 / 109 (6.42%)	12 / 114 (10.53%)	
occurrences (all)	7	12	
Renal and urinary disorders			
Week 16 Glycosuria	Additional description: Glycosuria at 16 weeks		
subjects affected / exposed	10 / 109 (9.17%)	9 / 114 (7.89%)	
occurrences (all)	10	9	
Month 6 Glycosuria	Additional description: Glycosuria at 6 months		
subjects affected / exposed	11 / 109 (10.09%)	13 / 114 (11.40%)	
occurrences (all)	11	13	
Month 12 Glycosuria	Additional description: Glycosuria at 12 months		
subjects affected / exposed	12 / 109 (11.01%)	17 / 114 (14.91%)	
occurrences (all)	12	17	
Month 24 Glycosuria	Additional description: Glycosuria at 24 months		
subjects affected / exposed	14 / 109 (12.84%)	19 / 114 (16.67%)	
occurrences (all)	14	19	
Endocrine disorders			
Week 16 Cushingoid Facies	Additional description: Cushingoid facies assessed at Week 16		

subjects affected / exposed	72 / 109 (66.06%)	77 / 114 (67.54%)	
occurrences (all)	72	77	
Month 6 Cushingoid Facies	Additional description: Cushingoid facies assessed at 6 months		
subjects affected / exposed	75 / 109 (68.81%)	79 / 114 (69.30%)	
occurrences (all)	75	79	
Month 12 Cushingoid Facies	Additional description: Cushingoid facies assessed at 12 months		
subjects affected / exposed	76 / 109 (69.72%)	81 / 114 (71.05%)	
occurrences (all)	76	81	
Month 24 Cushingoid Facies	Additional description: Cushingoid facies assessed at 24 months		
subjects affected / exposed	78 / 109 (71.56%)	83 / 114 (72.81%)	
occurrences (all)	78	83	
Metabolism and nutrition disorders			
Week 16 Increased Appetite	Additional description: Increased appetite at Week 16		
subjects affected / exposed	95 / 109 (87.16%)	98 / 114 (85.96%)	
occurrences (all)	95	98	
Month 6 Increased Appetite	Additional description: Increased appetite at 6 months		
subjects affected / exposed	98 / 109 (89.91%)	100 / 114 (87.72%)	
occurrences (all)	98	100	
Month 12 Increased Appetite	Additional description: Increased appetite at 12 months		
subjects affected / exposed	102 / 109 (93.58%)	104 / 114 (91.23%)	
occurrences (all)	102	104	
Month 24 Increased Appetite	Additional description: Increased appetite at 24 months		
subjects affected / exposed	103 / 109 (94.50%)	106 / 114 (92.98%)	
occurrences (all)	103	106	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2011	Protocol V2.0 - Change of definition of relapse. The decision to change the definition of relapse was made following widespread consultation with UK Paediatric Nephrologists. Whilst the definition of relapse originally proposed by the International Study of Kidney Disease in Childhood was 3 consecutive days of 2+ proteinuria, in clinical practice this has been replaced by 3 days of 3+ proteinuria. Every major UK Paediatric Nephrology centre uses this latter definition in the day to day management of their patients, and the most recent version of the major international textbook of Paediatric Nephrology also recommends this definition. In practice this makes little difference, as during relapses the large majority of patients rapidly develop very heavy proteinuria which is vastly in excess of both 2+ or 3+ proteinuria. However, we felt that it was important that the study used a definition that was appropriate to clinical practice in 2011. This decision to alter the definition of the primary end point will not impact upon any future decision by the Cochrane group to include the study into their meta-analysis. There are occasions where parents either intentionally or accidentally do not test their child's urine and relapse is not detected until the child becomes generally oedematous with a very low serum albumin level. This is more often the case in long established cases; in general in the early days parents are anxious and therefore take great care to test their child's urine on a regular basis. We have, however, decided to expand our definition of relapse to include children with generalised oedema and 3+ or more proteinuria, so that relapse treatment can be commenced straight away, reflecting routine clinical practice. It would be routine for such children to commence immediate relapse treatment rather than waiting for three consecutive days of 3+ proteinuria as the diagnosis of relapse is absolutely clear.
09 January 2014	Protocol V2.1 - The protocol has been amended to reflect the Chief Investigator's title change from a Doctor to Professor. A decision was made by the Chief Investigator to change the time the 10ml blood sample for research purposes could be collected from 'some point during the first year follow-up', to 'anytime during the patient's follow-up within the trial'. Extension to Recruitment Period - a monitoring meeting took place on 12th Feb 2013 to discuss the progress of the trial with the HTA. In June 2013 recruitment was behind target with 145 patients currently being randomised which was 79 patients below the target of 224 patients for June 2013, despite the number of participating centres being above the original target of 90. A decision was made to request funds to extend the recruitment period to allow the requisite number of patients to be recruited. At the rate of recruitment of 7 patients per month the original target of 224 patients would have been reached by June 2014. The study drop-out rate was also slightly higher than anticipated, with a drop-out rate of 15% rather than the expected 10% drop-out rate. Therefore the recruitment target was increased from 224 to 236 patients to ensure there were 200 analysable patients in total (100 in each arm). At a recruitment rate of 7 patients per month the 236 patients would be recruited by July 2014. We therefore wished to extend the recruitment period by 13 months and to increase the target number of patients to 236. A funding request was submitted to the HTA and approved. The trial should successfully reach its recruitment target of 236 by July 2014, providing the trial with sufficient patients to power the study to reach its research objectives. The protocol has been revised in light of the extended recruitment period and increased participant numbers.
18 August 2014	Protocol V2.2 - The protocol was amended to include an extension to the recruitment period from 37 to 40 months. Other minor administrative changes were also made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: