Clinical trial results:
Short course daily prednisolone therapy at the time of upper respiratory tract infection in children with relapsing steroid sensitive nephrotic syndrome; the PREDNOS 2 study.

Summary

EudraCT number	2012-003476-39
Trial protocol	GB
Global end of trial date	10 September 2020

Results information

Result version number	v1 (current)
This version publication date	21 April 2022
First version publication date	21 April 2022
Summary attachment (see zip file)	PREDNOS 2 HTA Report (HTA report.pdf) PREDNOS 2 JAMA publication (jamapediatrics_christian_2021_oi_210077_1639156054.50744.pdf)

Trial information

Trial identification

Sponsor protocol code	RG_12-188

Additional study identifiers

ISRCTN number	ISRCTN10900733
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	University of Birmingham Sponsor Reference: RG_12-188, NIHR HTA Grant Reference No.: 11/129/261, IRAS Project Code: 111990, CTA No.: 21761/0281/001-0001, REC Reference No.: 12/NW/0766

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
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Scientific contact	Dr Martin Christian, Nottingham Children’s Hospital, Martin.Christian@nuh.nhs.uk
Sponsor organisation name	University of Birmingham
Sponsor organisation address	Edgbaston, Birmingham, United Kingdom, B15 2TT
Public contact	Dr Martin Christian, Nottingham Children's Hospital, Martin.Christian@nuh.nhs.uk
Scientific contact	Dr Martin Christian, Nottingham Children's Hospital, Martin.Christian@nuh.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	25 September 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether a six day course of oral prednisolone given at the time of URTI reduces the incidence of first URTI-related relapse in children with relapsing steroid sensitive nephrotic syndrome.

Protection of trial subjects:

Research participants received a six day course of oral prednisolone each and every time they developed an URTI over the 12 month study period, which met the strict criteria laid down in the study protocol. The aim of this was to try and prevent the development of URTI-related relapse, necessitating the commencement of high dose daily prednisolone therapy. There was the risk that this course of action could increase overall steroid exposure without reducing relapse rate. We monitored patients every three months and carefully documented steroid-related adverse events, including impact on behaviour. Those children who experienced steroid toxicity during the course of the study had their background immunosuppressive therapy enhanced in an attempt to reduce relapse frequency.
There were no additional study visits for the purposes of the study alone. The three monthly visits were in keeping with routine care in children with relapsing nephrotic syndrome.
A single blood test was collected for the purposes of DNA studies. Where possible, this was collected at the time of venepuncture for routine clinical purposes. We ensured that patient discomfort was minimised through the use of topical anaesthetic creams, ethyl chloride spray, distraction therapy etc. in accordance with the individual child's preference. The volume of blood to be sampled (10ml) did not pose any risk re development of hypovolaemia or anaemia.

Background therapy:

Subjects were eligible if they were on any of the following four background therapies
- Subjects on no long-term immunosuppressive therapy;
- Subjects receiving long term maintenance prednisolone therapy at a dose of up to and including 15mg/m2 on alternate days. Note that this is the maximum dose at the time of recruitment – if children subsequently receive a higher dose e.g. after relapse, they can remain in the study;
- Subjects receiving long term maintenance prednisolone therapy at a dose of up to and including 15mg/m2 on alternate days in conjunction with other immunosuppressive therapies, including levamisole, ciclosporin, tacrolimus, MMF, mycophenolate sodium and azathioprine;
- Subjects receiving long-term immunosuppressive therapies, including levamisole, ciclosporin, tacrolimus, MMF, mycophenolate sodium and azathioprine without long term maintenance prednisolone therapy.

Evidence for comparator:

There is known to be a strong link between viral upper respiratory tract infection (URTI - the common cold) and the development of relapse of nephrotic syndrome. Three previous small studies have suggested that the use of a short course of daily prednisolone at the time of URTI reduces the rate of

disease relapse. The PREDNOS 2 study determined whether the use of such therapy effectively and safely reduced the rate of relapse in a large population of UK children. Children were randomised with relapsing SSNS to receive either 6 days of daily prednisolone or placebo tablets (and so continue unchanged on their existing therapy, the current standard of care) each time they develop a URTI over a 12 month period.

Actual start date of recruitment	19 March 2013
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: 365
Worldwide total number of subjects	365
EEA total number of subjects	0

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)	0
Children (2-11 years)	315
Adolescents (12-17 years)	50
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was performed from Feb 1, 2013, to Jan 31, 2020, in 122 UK paediatric departments, consisting of 13 specialized paediatric nephrology and 109 general paediatric units. In the UK most children with SSNS are cared for by general paediatricians and only those with a more complicated disease course are seen by paediatric nephrologist.

Pre-assignment

Screening details:

Participants were screened using the eligibility criteria as specified in the protocol. Formal screening logs were requested and in keeping with other studies they were not well kept. An estimate of approximately 1/3 of eligible patients entered the PREDNOS 2 trial.

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, 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 dispatch the pots of trial treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active

Arm description:

Daily prednisolone 15mg/m2 for a total of 6 days commenced once criteria for URTI have been met.

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:

Subjects who are receiving a long term maintenance prednisolone dose of up to and including 15mg/m2 on alternate days (including those not on maintenance prednisolone therapy) at the time of development of URTI will receive the following;
Active treatment arm - prednisolone 15mg/m2 daily for a total of six days, through the use of additional prednisolone study drug tablets. Subjects who are receiving a prednisolone dose of greater than 15mg/m2 on alternate days at the time of development of URTI will receive the following; Active treatment arm - prednisolone at alternate daily dose given daily for a total of six days, through the use of additional prednisolone study drug tablets. Once the six day course of study drug is complete, the subject will revert to their previous long term maintenance prednisolone dose (or no prednisolone if previously not receiving this). This will be repeated each and every time the subject develops an URTI meeting the designated criteria over the 12 months.

Arm title	Placebo

Arm description:

Daily placebo 15mg/m2 for a total of 6 days commenced once criteria for URTI have been met.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	N/A
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Daily placebo for a total of 6 days commenced once criteria for URTI have been met. Subjects who are receiving a long term maintenance prednisolone dose of up to and including 15mg/m2 on alternate days (including those not on maintenance prednisolone therapy) at the time of development of URTI will receive – No change to therapy through the use of placebo study drug tablets for a total of six days. Subjects who are receiving a prednisolone dose of greater than 15mg/m2 on alternate days at the time of development of URTI will receive; No change to therapy through the use of placebo study drug tablets for a total of six days. Once the six day course of study drug is complete, the subject will revert to their previous long term maintenance prednisolone dose (or no prednisolone if previously not receiving this). This will be repeated each and every time the subject develops an URTI meeting the designated criteria over the 12 month study period.

Number of subjects in period 1	Active	Placebo
Started	182	183
Completed	134	137
Not completed	48	46
Did not have URTI	48	46

Baseline characteristics

Reporting groups	
Reporting group title	Active
Reporting group description:	
Daily prednisolone 15mg/m2 for a total of 6 days commenced once criteria for URTI have been met.	

Reporting group title	Placebo
Reporting group description:	
Daily placebo 15mg/m2 for a total of 6 days commenced once criteria for URTI have been met.	

Reporting group values	Active	Placebo	Total
Number of subjects	182	183	365
Age categorical 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)	0	0	0
Children (2-11 years)	158	157	315
Adolescents (12-17 years)	24	26	50
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	7.6	7.6	
standard deviation	± 3.5	± 3.5	-
Gender categorical Units: Subjects			
Female	65	62	127
Male	117	121	238
Ethnicity Units: Subjects			
British	118	115	233
Irish	0	4	4
Other white background	12	5	17
African	2	4	6
Other black British background	2	3	5
Indian	11	10	21
Pakistani	12	14	26
Bangladeshi	6	6	12
Sri Lankan	3	1	4
Other Asian background	3	3	6
White and Black Caribbean	1	2	3
White and Black African	1	4	5
White and Asian	5	5	10

Other mixed background	2	2	4
Chinese	0	1	1
Other ethnic group	2	3	5
Not stated	2	1	3
BMI percentile Units: Subjects			
Underweight (<5th)	0	2	2
Healthy (5th - 84th)	91	90	181
Overweight (85th - 94th)	34	34	68
Obese (>or equal to 95th)	57	57	114
BMI Percentile Units: Percentile			
median	85	84.8	
inter-quartile range (Q1-Q3)	64.4 to 97.2	65.2 to 96.9	-
Prednisolone dose			
(mg on alternate days)			
Units: mg			
arithmetic mean	9.2	8.8	
standard deviation	± 3.8	± 3.4	-
Age at diagnosis of nephrotic syndrome Units: Years			
arithmetic mean	4.4	4.6	
standard deviation	± 2.5	± 2.8	-
Time from last relapse to randomisation Units: Days			
median	89	91	
inter-quartile range (Q1-Q3)	58 to 138	61 to 126	-
Time from second relapse to randomisation Units: Days			
median	209.5	189	
inter-quartile range (Q1-Q3)	148 to 287	146 to 264	-

Subject analysis sets

Subject analysis set title	Modified Intention to Treat Population Active
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A total of 365 children with relapsing steroid-sensitive nephrotic syndrome were randomised (1 : 1) according to a minimisation algorithm based on background treatment. Eighty children completed 12 months of follow-up without an upper respiratory tract infection. Thirty-two children were withdrawn from the trial (14 prior to an upper respiratory tract infection), leaving a modified intention-to-treat analysis population of 271 children (134 and 137 children in the prednisolone and placebo arms, respectively).

Subject analysis set title	Modified Intention to Treat Population Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A total of 365 children with relapsing steroid-sensitive nephrotic syndrome were randomised (1 : 1) according to a minimisation algorithm based on background treatment. Eighty children completed 12 months of follow-up without an upper respiratory tract infection. Thirty-two children were withdrawn from the trial (14 prior to an upper respiratory tract infection), leaving a modified intention-to-treat analysis population of 271 children (134 and 137 children in the prednisolone and placebo arms, respectively).

Reporting group values	Modified Intention to Treat Population Active	Modified Intention to Treat Population Placebo	
Number of subjects	134	137	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)	116	119	
Adolescents (12-17 years)	18	18	
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	7.7	7.5	
standard deviation	± 3.6	± 3.5	
Gender categorical Units: Subjects			
Female	51	46	
Male	83	91	
Ethnicity Units: Subjects			
British	85	88	
Irish	0	2	
Other white background	11	2	
African	1	3	
Other black British background	1	2	
Indian	9	7	
Pakistani	9	9	
Bangladeshi	4	4	
Sri Lankan	2	1	
Other Asian background	3	2	
White and Black Caribbean	0	2	
White and Black African	1	4	
White and Asian	3	5	
Other mixed background	1	2	
Chinese	0	0	
Other ethnic group	2	3	
Not stated	2	1	
BMI percentile Units: Subjects			
Underweight (<5th)	0	0	
Healthy (5th - 84th)	67	64	
Overweight (85th - 94th)	24	30	
Obese (>or equal to 95th)	41	43	

BMI Percentile			
Units: Percentile			
median	84.1	86.4	
inter-quartile range (Q1-Q3)	63.7 to 96.9	68.4 to 97	
Prednisolone dose			
(mg on alternate days)			
Units: mg			
arithmetic mean	9.2	8.4	
standard deviation	± 3.7	± 3.1	
Age at diagnosis of nephrotic syndrome			
Units: Years			
arithmetic mean	4.4	4.4	
standard deviation	± 2.5	± 2.8	
Time from last relapse to randomisation			
Units: Days			
median	90	87	
inter-quartile range (Q1-Q3)	58 to 143	58 to 126	
Time from second relapse to randomisation			
Units: Days			
median	209.5	189	
inter-quartile range (Q1-Q3)	153 to 287	146 to 252	

End points

End points reporting groups

Reporting group title	Active

Reporting group description:

Daily prednisolone 15mg/m2 for a total of 6 days commenced once criteria for URTI have been met.

Reporting group title	Placebo

Reporting group description:

Daily placebo 15mg/m2 for a total of 6 days commenced once criteria for URTI have been met.

Subject analysis set title	Modified Intention to Treat Population Active
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A total of 365 children with relapsing steroid-sensitive nephrotic syndrome were randomised (1 : 1) according to a minimisation algorithm based on background treatment. Eighty children completed 12 months of follow-up without an upper respiratory tract infection. Thirty-two children were withdrawn from the trial (14 prior to an upper respiratory tract infection), leaving a modified intention-to-treat analysis population of 271 children (134 and 137 children in the prednisolone and placebo arms, respectively).

Subject analysis set title	Modified Intention to Treat Population Placebo
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A total of 365 children with relapsing steroid-sensitive nephrotic syndrome were randomised (1 : 1) according to a minimisation algorithm based on background treatment. Eighty children completed 12 months of follow-up without an upper respiratory tract infection. Thirty-two children were withdrawn from the trial (14 prior to an upper respiratory tract infection), leaving a modified intention-to-treat analysis population of 271 children (134 and 137 children in the prednisolone and placebo arms, respectively).

Primary: Proportion of patients experiencing an URTI related relapse

End point title	Proportion of patients experiencing an URTI related relapse

End point description:

All outcome analyses were carried out on the modified ITT population of 271 children and excluded the 80 children who completed 12 months of follow-up without having had an URTI and the 14 children who were withdrawn without having had an URTI. The median time from randomisation to first URTI was 61 (IQR 21–126) days in the intervention arm and 54 (IQR 23–98) days in the placebo arm. There were 384 URTIs and 82 URRs in the intervention arm and 407 URTIs and 82 URRs in the placebo arm. One patient in the placebo arm had an URTI, but no information was provided on whether or not they had a URR and so their data were classed as missing. Three patients in the intervention arm and five patients in the placebo arm had URTIs but withdrew before the 12-month follow-up and did not report any URR for any time points for which they provided data. These patients were excluded from the primary analysis, but were included in a sensitivity analysis.

End point type	Primary

End point timeframe:

Time to URTI and then any URTI related relapse within the 12 month assessment period.

End point values	Modified Intention to Treat Population Active	Modified Intention to Treat Population Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134	137		

Units: Proportion				
Yes	56	58		
No	75	73		

Statistical analyses

Statistical analysis title	Proportion of patients experiencing an URR
Statistical analysis description:	
Proportion of patients experiencing an URTI-Related Relapse (URR)	
Comparison groups	Modified Intention to Treat Population Active v Modified Intention to Treat Population Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7
Method	Binomial Model with Identity LinkFuntion
Parameter estimate	Risk difference (RD)
Point estimate	-0.024
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.09
Variability estimate	Standard error of the mean

Secondary: URTI-related relapse rate

End point title	URTI-related relapse rate
End point description:	
End point type	Secondary
End point timeframe:	
Time to URTI and then time to URTI related relapse in the 12 month study period.	

End point values	Modified Intention to Treat Population Active	Modified Intention to Treat Population Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134	137		
Units: Number of relapses				
None	78	78		
One	36	41		
Two	15	10		
Three	4	7		

Four	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients experiencing any relapse

End point title	Proportion of patients experiencing any relapse

End point description:

Proportion of patients experiencing any relapse (URTI and non-URTI related)

End point type	Secondary

End point timeframe:

Time to relapse in the 12 month study period

End point values	Modified Intention to Treat Population Active	Modified Intention to Treat Population Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134	137		
Units: Relapses				
No	41	34		
Yes	91	98		

Statistical analyses

No statistical analyses for this end point

Secondary: Relapse rate

End point title	Relapse rate

End point description:

End point type	Secondary

End point timeframe:

Time to relapse in the 12 month study period

End point values	Modified Intention to Treat Population Active	Modified Intention to Treat Population Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134	137		
Units: Relapses				
None	43	38		
One	28	39		
Two	24	24		
Three	22	11		
Four	11	14		
Five	6	5		
Greater or equal to six	0	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients who had escalation of background immunosuppressant therapy

End point title	Proportion of patients who had escalation of background immunosuppressant therapy

End point description:

End point type	Secondary

End point timeframe:

Escalation of therapy in the 12 month study period.

End point values	Modified Intention to Treat Population Active	Modified Intention to Treat Population Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134	137		
Units: Escalation (Y/N)				
No	72	71		
Yes	58	57		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients who had reduction of background immunosuppressant therapy

End point title	Proportion of patients who had reduction of background immunosuppressant therapy

End point description:

End point type	Secondary

End point timeframe:

Reduction in 12 month study period

End point values	Modified Intention to Treat Population Active	Modified Intention to Treat Population Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134	137		
Units: Reduction (Y/N)				
No	73	67		
Yes	55	62		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative prednisolone dose

End point title	Cumulative prednisolone dose

End point description:

End point type	Secondary

End point timeframe:

Cumulative dose in 12 month study period

End point values	Modified Intention to Treat Population Active	Modified Intention to Treat Population Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	134	137		
Units: mg				
median (inter-quartile range (Q1-Q3))	2060 (1128 to 3355)	1880 (1115 to 3295)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Occurring over the 12 month study period and up to 3 months post treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Prednisolone
Reporting group description: -	

Serious adverse events	Placebo	Prednisolone	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 137 (22.63%)	29 / 134 (21.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Blood/Bone marrow			
subjects affected / exposed	1 / 137 (0.73%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergy			
subjects affected / exposed	2 / 137 (1.46%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal			
subjects affected / exposed	4 / 137 (2.92%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Influenza			

subjects affected / exposed	1 / 137 (0.73%)	2 / 134 (1.49%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin			
subjects affected / exposed	2 / 137 (1.46%)	0 / 134 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrotic syndrome			
subjects affected / exposed	20 / 137 (14.60%)	19 / 134 (14.18%)	
occurrences causally related to treatment / all	2 / 33	2 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal/Soft tissue			
subjects affected / exposed	0 / 137 (0.00%)	1 / 134 (0.75%)	
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	16 / 137 (11.68%)	16 / 134 (11.94%)	
occurrences causally related to treatment / all	2 / 28	1 / 22	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Prednisolone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 137 (83.94%)	106 / 134 (79.10%)	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	33 / 137 (24.09%)	35 / 134 (26.12%)	
occurrences (all)	33	35	
Skin and subcutaneous tissue disorders			

Striae			
subjects affected / exposed	8 / 137 (5.84%)	9 / 134 (6.72%)	
occurrences (all)	8	9	
Hypertrichosis			
subjects affected / exposed	18 / 137 (13.14%)	16 / 134 (11.94%)	
occurrences (all)	18	16	
Acne			
subjects affected / exposed	11 / 137 (8.03%)	12 / 134 (8.96%)	
occurrences (all)	11	12	
Psychiatric disorders			
Poor behaviour			
subjects affected / exposed	74 / 137 (54.01%)	60 / 134 (44.78%)	
occurrences (all)	74	60	
Endocrine disorders			
Cushingoid facies			
subjects affected / exposed	41 / 137 (29.93%)	41 / 134 (30.60%)	
occurrences (all)	41	41	
Glycosuria			
subjects affected / exposed	8 / 137 (5.84%)	11 / 134 (8.21%)	
occurrences (all)	8	11	
Metabolism and nutrition disorders			
Increased appetite			
subjects affected / exposed	80 / 137 (58.39%)	68 / 134 (50.75%)	
occurrences (all)	80	68	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2014	Protocol release V1.2 The protocol has been amended to reflect the Chief Investigator's title change from a Doctor to Professor. Membership of the Trial Steering Committee information has been updated Prof Timothy Barrett has been removed from the Data Monitoring Committee. A decision has been made by the Chief Investigator to change the wording in the exclusion criteria due to confusion at some centres regarding the background prednisolone dose the patient should be on at the time of randomisation. The exclusion criteria regarding subjects on 'a long term maintenance prednisolone dose of greater than 15mg/m2 on alternate days at time of recruitment' will be changed to subjects on a 'prednisolone dose of greater than 15mg/m2 on alternate days at time of recruitment'.The PREDNOS 2 study trial schema wording has been corrected to show patient's in the active treatment arm will have ' prednisolone administered daily for 6 days commenced within 24 hours of the criteria for an URTI being met', in place of 'prednisolone administered daily for 6 days commenced within 24 hours of onset of first URTI'. The definition of a relapse has been made consistent throughout the protocol. The study visit schedule has been amended to state a blood sample is required from all patients in the study, including those who previously participated in the blood sample for the PREDNOS study (giving a blood sample is optional). The Statistical Analysis Section has been updated with further details. There have been no changes to the planned analyses but the explanation of the analyses has been expanded upon.
09 June 2015	Release of protocol V1.3 Protocol Amendment: • The protocol has been amended to reflect the increase in recruitment period from 2 to 3 years. • The total study duration has increased from 4 to 5 years. • Section 4.7 regarding the commencement of study drug has been amended to state 'parents will be asked to contact their local study site before or within 24 hours of commencing study drug'. • Other minor and administrative amendments.

16 June 2017	Release of protocol V2.0 • Sample size increased from 300 patients to 360 patients. • Increase in recruitment period from 3 years to 5 years and 1 month. • Total study duration has increased from 5 years to 7 years and 1 month. • Primary outcome measure has been refined to 'First URTI-related relapse of nephrotic syndrome during the 12 month follow-up'. • The RSI wording has been amended to state section 4.8 of the Wockhardt UK Ltd SmPC dated 31st March 2003 is the current RSI for the study. • Parents/patients are instructed to contact Birmingham Children's Hospital pharmacy to confirm receipt of study medication. Pharmacy are instructed to document when the parents/patients confirm receipt of the study medication. • In Section 4.7 of the protocol, further instruction is provided on the use of the Advice Letter to Parents/Patients and a reminder that any contact between the site and parents/patients should be recorded in the medical notes. • In Section 4.12 the study visit schedule has been amended to include tablet count details on the PREDNOS 2 Case Report Forms (CRFs) at each assessment visit. • Section 4.16 has been amended to state the investigator must check and sign the Randomisation Notepad to confirm that the eligibility criteria have been met. • In Section 4.20 further details on how to record the use of patient diaries has been added. • Section 4.22, information on the completion of CRFs and questionnaires, and source data has been amended. • Section 4.25 and Appendix 3 amended to reflect changes to the emergency unblinding process. • Section 4.28 amended to reflect the changes to the sample size from 300 to 360 patients. • Section 4.29 updated to reflect refinement to the primary outcome measure and statistical analysis. • Section 5.0 Safety Assessment and Report includes a change to expectedness assessment, which should be carried out by the Chief Investigator and not the local investigator
03 October 2018	Release of protocol V3.0 • Prof Nicholas Webb has been replaced by Dr Martin Christian as Chief Investigator, and the associated contact details have been updated. • The protocol has been amended to reflect the increase in recruitment period from 5 years and 1 month to 5 years and 11 months. • The total study duration has increased from 7 years and 1 month to 7 years and 10 months. Please note – the apparent difference in extension times for recruitment period vs whole study duration is actually due to a miscalculation. The first patient was recruited after 5 months of set up when 6 months had initially been allowed for and subsequent extensions used the assumed 6 months of set up to calculate extension times (this was only spotted whilst preparing this amendment). • The protocol has been updated to reflect both the General Data Protection Regulation 2018 and the Data Protection Act 2018. • Updated sponsor trust name to reflect trust merger.

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.

A larger number of children than expected did not have an upper respiratory tract infection and the sample size attrition rate was adjusted accordingly during the trial.

Notes: