



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 |
| Sponsor organisation address | Room 119, Aston Webb Building, Birmingham, United Kingdom, B15 2TT |
| 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 |
| Sponsor organisation name | Manchester University NHS Foundation Trust (was Central Manchester University Hospitals NHS Foundation Trust) |
| 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 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/m ² /day (maximum dose 80mg) for four weeks followed by 40mg/m ² (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/m ² /day (maximum 80mg) for four weeks followed by 60mg/m ² (maximum 60mg) on alternate days for two weeks with a subsequent gradual reduction in dose over a total of 12 weeks (tapering by 10mg/m ² 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/m ² /day (maximum dose 80mg) for four weeks followed by 40mg/m ² (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/m ² /day (maximum 80mg) for four weeks followed by 60mg/m ² (maximum 60mg) on alternate days for two weeks with a subsequent gradual reduction in dose over a total of 12 weeks (tapering by 10mg/m ² 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 subjects affected / exposed occurrences (all) | Additional description: Cataract at 12 months | | |
| | 1 / 109 (0.92%) 1 | 0 / 114 (0.00%) 0 | |
| Month 24 Cataract subjects affected / exposed occurrences (all) | Additional description: Cataract at 24 months | | |
| | 1 / 109 (0.92%) 1 | 1 / 114 (0.88%) 1 | |
| Gastrointestinal disorders | | | |
| Week 16 Abdominal Pain subjects affected / exposed occurrences (all) | Additional description: Abdominal pain at 16 weeks | | |
| | 31 / 109 (28.44%) 31 | 28 / 114 (24.56%) 28 | |
| Month 6 Abdominal Pain subjects affected / exposed occurrences (all) | Additional description: Abdominal pain at 6 months | | |
| | 35 / 109 (32.11%) 35 | 38 / 114 (33.33%) 38 | |
| Month 12 Abdominal Pain subjects affected / exposed occurrences (all) | Additional description: Abdominal pain at 12 months | | |
| | 46 / 109 (42.20%) 46 | 44 / 114 (38.60%) 44 | |
| Month 24 Abdominal Pain subjects affected / exposed occurrences (all) | Additional description: Abdominal pain at 24 months | | |
| | 51 / 109 (46.79%) 51 | 49 / 114 (42.98%) 49 | |
| Skin and subcutaneous tissue disorders | | | |
| Week 16 Striae subjects affected / exposed occurrences (all) | Additional description: Striae assessed at Week 16 | | |
| | 3 / 109 (2.75%) 3 | 8 / 114 (7.02%) 8 | |
| Month 6 Striae subjects affected / exposed occurrences (all) | Additional description: Striae assessed at 6 months | | |
| | 4 / 109 (3.67%) 4 | 11 / 114 (9.65%) 11 | |
| Month 12 Striae subjects affected / exposed occurrences (all) | Additional description: Striae assessed at 12 months | | |
| | 6 / 109 (5.50%) 6 | 11 / 114 (9.65%) 11 | |
| Month 24 Striae subjects affected / exposed occurrences (all) | Additional description: Striae assessed at 24 months | | |
| | 7 / 109 (6.42%) 7 | 14 / 114 (12.28%) 14 | |
| Week 16 Hypertrichosis subjects affected / exposed occurrences (all) | Additional description: Hypertrichosis assessed at Week 16 | | |
| | 25 / 109 (22.94%) 25 | 34 / 114 (29.82%) 34 | |
| Month 6 Hypertrichosis | Additional description: Hypertrichosis assessed at 6 months | | |

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 18 April 2011 | <p>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.</p> |
| 09 January 2014 | <p>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.</p> |
| 18 August 2014 | <p>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.</p> |

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.

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| None reported |
|---------------|

Notes: