



Clinical trial results:

Oral steroids for the resolution of otitis media with effusion in children study (OSTRICH)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-005123-32 |
| Trial protocol | GB |
| Global end of trial date | 27 April 2017 |

Results information

| | |
|-----------------------------------|--------------------------------------|
| Result version number | v1 (current) |
| This version publication date | 29 December 2018 |
| First version publication date | 29 December 2018 |
| Summary attachment (see zip file) | HTA report for OSTRICH (3021508.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | SPON1030-11 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN49798431 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Cardiff University |
| Sponsor organisation address | McKensie House, Newport Road, Cardiff, United Kingdom, CF24 0DE |
| Public contact | Trial Manager, Cardiff University, 0044 029 20 687 609, OSTRICH@cardiff.ac.uk |
| Scientific contact | Trial Manager, Cardiff University, 0044 02920 687 609, OSTRICH@cardiff.ac.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 | 15 September 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 April 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 April 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the clinical and cost effectiveness of a 7 day course of oral prednisolone (steroid) on improving hearing in the short term in children with bilateral OME with confirmed hearing loss for at least 3 months.

Protection of trial subjects:

The IDMC for the OSTRICH trial was build-up to safeguard the interests of the OSTRICH trial participants, potential participants, investigator and sponsor; to assess the safety and efficacy of the trial interventions, and to monitor the trial's overall conduct, and protect its validity and credibility. Six IDMC meetings were held (21/03/2013, 08/07/2014, 16/09/2014, 21/01/2015, 25/06/2015 and 08/03/2016). The IDMC received and reviewed the progress and accruing data of this trial and provided advice on the conduct of the trial to the Trial Steering Committee (TSC).

Potential risk of clinical deterioration during the time between the patient's consultation with their ENT clinician and the end of the study treatment period was minimised as patients could follow their usual care pathway at 5 weeks post randomisation.

There was a small risk of side effects (such as gastrointestinal disturbance or behavioural effects) from the trial medication, which were explained to participating parents/carers(s) and children (where appropriate). All adverse event were monitored and 24 hour emergency unblinding was available.

The Audiometry, Tympanometry and Otoscopy may cause minimal discomfort or intrusion in young children. However, these assessments are normally be conducted in usual care, and are conducted by trained ENT clinicians and Audiologists experienced in working with this age group, who would have been able to minimise any distress or discomfort the children may have experienced.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------------------------------|
| Actual start date of recruitment | 20 March 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy, Scientific research |
| Long term follow-up duration | 1 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 380 |
| Worldwide total number of subjects | 380 |
| EEA total number of subjects | 380 |

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) | 380 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Children were identified and followed up in ear, nose and throat (ENT) outpatient or Paediatric Audiology and Audiovestibular Medicine (AVM) clinics in Wales and England between 20th March 2014 and 5th April 2016. Sites were selected based on their recruitment potential and membership of clinical research networks.

Pre-assignment

Screening details:

1. Eligible patients identified in secondary care centres.
2. Ear, Nose and Throat (ENT)/ /audiovestibular medicine (AVM) clinician checks eligibility and takes consent.
3. Pharmacy dispenses pre-randomised trial medication by selecting next sequentially ordered trial pack.

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, Data analyst, Carer, Assessor |

Blinding implementation details:

Sequential pack numbers were randomly assigned to oral steroid or placebo (1:1) using computer generated random permuted block sizes stratified by site and child's age group (2-5, 6-8 years old). Recruited children were allocated the next sequentially numbered trial pack at each site pharmacy. Children, parents/legal guardians, clinical staff and the trial team (including the statistician) were all blinded to treatment allocation.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Seven day course of placebo matched for packaging, colour, solubility, and consistency, as a single daily dose of 20mg or 30mg for children aged 2-5 years or 6-8 years respectively.

| | |
|--|-----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Participants in the placebo group received a 7-day course of oral soluble placebo. The placebo used in this trial was matched for consistency, colour and solubility, as well as visually and in its packaging.

| | |
|------------------|--------------|
| Arm title | Oral Steroid |
|------------------|--------------|

Arm description:

Seven day course of oral soluble Prednisolone, as a single daily dose of 20mg or 30mg for children aged 2-5 years or 6-8 years respectively.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Oral soluble prednisolone (oral steroid) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Participants in the active treatment group received a 7-day course of oral soluble prednisolone.

| Number of subjects in period 1 | Placebo | Oral Steroid |
|--|---------|--------------|
| Started | 187 | 193 |
| 5 weeks post randomisation | 180 | 183 |
| 6 months post randomisation | 166 | 174 |
| 12 months post randomisation | 162 | 170 |
| Completed | 162 | 170 |
| Not completed | 25 | 23 |
| attended clinic but missing outcome data | 10 | 2 |
| Lost to follow-up | 15 | 21 |

Baseline characteristics

Reporting groups

| | |
|---|--------------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Seven day course of placebo matched for packaging, colour, solubility, and consistency, as a single daily dose of 20mg or 30mg for children aged 2-5 years or 6-8 years respectively. | |
| Reporting group title | Oral Steroid |
| Reporting group description: | |
| Seven day course of oral soluble Prednisolone, as a single daily dose of 20mg or 30mg for children aged 2-5 years or 6-8 years respectively. | |

| Reporting group values | Placebo | Oral Steroid | Total |
|-----------------------------|---------|--------------|-------|
| Number of subjects | 187 | 193 | 380 |
| Age categorical | | | |
| Age of child at recruitment | | | |
| Units: Subjects | | | |
| 2-5 years | 133 | 131 | 264 |
| 6-8 years | 54 | 62 | 116 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 5.08 | 5.30 | |
| standard deviation | ± 1.60 | ± 1.60 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 85 | 84 | 169 |
| Male | 102 | 109 | 211 |

End points

End points reporting groups

| | |
|---|--------------|
| Reporting group title | Placebo |
| Reporting group description: Seven day course of placebo matched for packaging, colour, solubility, and consistency, as a single daily dose of 20mg or 30mg for children aged 2-5 years or 6-8 years respectively. | |
| Reporting group title | Oral Steroid |
| Reporting group description: Seven day course of oral soluble Prednisolone, as a single daily dose of 20mg or 30mg for children aged 2-5 years or 6-8 years respectively. | |

Primary: 5 week follow-up

| | |
|---------------------------------|------------------|
| End point title | 5 week follow-up |
| End point description: | |
| End point type | Primary |
| End point timeframe: 5 weeks | |

| End point values | Placebo | Oral Steroid | | |
|------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 180 | 183 | | |
| Units: resolution of hearing | | | | |
| resolution of hearing | 59 | 73 | | |
| Hearing not resolved | 121 | 110 | | |

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Resolution of hearing |
| Comparison groups | Placebo v Oral Steroid |
| Number of subjects included in analysis | 363 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.136 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.36 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 2.11 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Data on adverse events was collected daily during the 5 day course of trial medication and then weekly up to 5 weeks post randomisation.

Adverse event reporting additional description:

All adverse events were recorded by parents in a symptom diary, with each symptom being rated from 0 to 6 by parents.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|---------------|
| Dictionary name | OSTRICH Diary |
|-----------------|---------------|

| | |
|--------------------|-----|
| Dictionary version | 1.9 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Adverse Events |
|-----------------------|----------------|

Reporting group description: -

| Serious adverse events | Adverse Events | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 380 (0.26%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma attack | | | |
| subjects affected / exposed | 1 / 380 (0.26%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Adverse Events | | |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 47 / 380 (12.37%) | | |
| Gastrointestinal disorders | | | |
| Digestion | Additional description: increased or low appetite, diarrhoea, constipation, nausea | | |
| subjects affected / exposed | 16 / 380 (4.21%) | | |
| occurrences (all) | 16 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|--|---|--|--|
| Respiratory tract infection subjects affected / exposed occurrences (all) | Additional description: coughs, colds, headaches | | |
| | 22 / 380 (5.79%) | | |
| | 22 | | |
| Psychiatric disorders Behaviour subjects affected / exposed occurrences (all) | Additional description: hyperactive, tired, frustration, sleep walking, change in behaviour | | |
| | 11 / 380 (2.89%) | | |
| | 11 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 11 July 2013 | <p>Substantial amendment - protocol version 2.0</p> <ul style="list-style-type: none">· Amendment made to where follow up visits will be conducted: e.g. followed up in ENT or Audiology outpatient clinics and Figure 1 amended,· Additions made to inclusion criteria: First time in the OSTRICH trial, ability of parent/carer to understand and give informed consent, does not already have grommets (ventilation tubes),· Additions made to exclusion criteria: Ear infection, Kartagener's or Primary Ciliary Dyskinesia, existing known sensory hearing loss, undergoing cancer treatment, on a waiting list for grommet surgery and anticipates having surgery within 5 weeks and unwilling to delay it,· Pharmacovigilance section amended to include section on expectedness, clarification on who is responsible for assessing causality and clarification of timeline for SUSARs e.g. 'day zero is defined as the date the SAE form is initially received at SEWTU'.· Additional procedure added to 5 week follow-up: At the 5 week follow up appointment any unused trial medication will be collected and returned to pharmacy for disposal. |
| 14 November 2013 | <p>Substantial amendment - protocol version 3.0</p> <ul style="list-style-type: none">· Rewording made to inclusion/ exclusion criteria: the inclusion criterion 'does not already have grommets (ventilation tubes)' changed to the exclusion criterion of 'child already has grommets (ventilation tubes)',· Changes to study procedure: a designated member of the OSTRICH team (where possible) or the participant's parent will collect the Trial pack from Pharmacy,· Unblinding telephone number added,· Amendment made to the different options that a parent can choose when withdrawing their child from the study,· Adverse events CRF completed at 5 week follow up as well as in parent diary to ensure all non-serious adverse reactions and events are recorded,· Changes to study procedure: Data linkage used to identify healthcare consultations during the 12 month follow up period in secondary care and primary care (where possible),· Timeframe windows for follow up added e.g. + 1 week for 5 week follow up, +/- 2 weeks for 6 and 12 month follow ups,· Pharmacovigilance section amended to include section on expectedness, clarification on who is responsible for assessing causality and clarification of timeline for SUSARs e.g. 'day zero is defined as the date the SAE form is initially received at SEWTU'. |
| 10 April 2014 | <p>Substantial amendment - protocol version 4.0</p> <ul style="list-style-type: none">· Addition of sub-study on qualitative sub-study will explore parents' understanding of the treatment options available to them and the views about the role of shared decision making in the context of managing glue ear, as well as their views on the use of oral steroids for glue ear.· Addition to 'supply, packaging, storage and reconciliation of trial medication' section, to say there is overage and extra tablets are to be returned at the 5 week follow up appointment. |
| 12 June 2014 | <p>Substantial amendment</p> <p>Change to study documentation only</p> <p>Consent form and Information Sheet.</p> |

| | |
|-------------------|---|
| 17 June 2014 | Substantial amendment Adding new sites |
| 03 July 2014 | Substantial amendment Adding new sites |
| 07 August 2014 | Substantial amendment Adding new sites |
| 17 September 2014 | Substantial amendment Adding new sites |
| 11 November 2014 | Substantial amendment Adding new sites |
| 30 January 2015 | Substantial amendment Removal of site. Two NHS trust name changes. Addition of Patient identification centre. |
| 13 April 2015 | Substantial amendment - protocol version 5.0. 2oc Temperature tolerance in reporting of temperature excursions. |
| 09 July 2015 | Substantial amendment - protocol version 6.0. Exclusion criteria added – no live vaccines 4 weeks prior to recruitment Addition of exploratory analysis to assess association between baseline hearing threshold and quality of life. Parent information sheet - amended to include that child should not have a live vaccine four weeks prior to recruitment. SmPC for prednisolone has been updated- Marketing Authorisation holder and Marketing Authorisation number has changed. |
| 18 August 2015 | Substantial amendment Adding new site |
| 22 October 2015 | Substantial amendment Changes to Site: Singleton Hospital, Swansea. Recruitment at Singleton Hospital will be moving to Morriston Hospital. |
| 23 October 2015 | Substantial amendment - protocol version 6.1. Exclusion criteria amended – no live vaccines 4 weeks prior to recruitment if under 3 years of age. Parent information sheet - amended to include that child should not have a live vaccine four weeks prior to recruitment if aged under 3 years old, and advised that if the child is under 3 years of age they are not given any immunisations whilst they are taking the study treatment and for 1 month after study participation. Consent Form –The Parent Information Sheet that is referred to on the Consent form has been amended with the new version/date. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26931619>