



## 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
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##### 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 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:

<b>Subjects enrolled per age group</b>	
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
<b>Arm title</b>	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.

<b>Arm title</b>	Oral Steroid
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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

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**Dosage and administration details:**

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

<b>Number of subjects in period 1</b>	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
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### Dictionary used

Dictionary name	OSTRICH Diary
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Dictionary version	1.9
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### Reporting groups

Reporting group title	Adverse Events
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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"><li>· Amendment made to where follow up visits will be conducted: e.g. followed up in ENT or Audiology outpatient clinics and Figure 1 amended,</li><li>· 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),</li><li>· 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,</li><li>· 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'.</li><li>· 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.</li></ul>
14 November 2013	<p>Substantial amendment - protocol version 3.0</p> <ul style="list-style-type: none"><li>· 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)',</li><li>· 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,</li><li>· Unblinding telephone number added,</li><li>· Amendment made to the different options that a parent can choose when withdrawing their child from the study,</li><li>· 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,</li><li>· 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),</li><li>· Timeframe windows for follow up added e.g. + 1 week for 5 week follow up, +/- 2 weeks for 6 and 12 month follow ups,</li><li>· 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'.</li></ul>
10 April 2014	<p>Substantial amendment - protocol version 4.0</p> <ul style="list-style-type: none"><li>· 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.</li><li>· 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.</li></ul>
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:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported

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## **Online references**

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