Clinical trial results:
What is the clinical and cost effectiveness of benzocaine/phenazone ear drops for reducing antibiotic consumption and ear pain in children aged between 6 months and 10 years presenting to primary care with acute otitis media (AOM)? An individually randomised, placebo controlled three-arm superiority trial with cost-effectiveness analysis, qualitative evaluation and a parallel observational cohort study.

Summary

EudraCT number	2014-004016-11
Trial protocol	GB
Global end of trial date	19 March 2019

Results information

Result version number	v1 (current)
This version publication date	26 October 2019
First version publication date	26 October 2019

Trial information

Trial identification

Sponsor protocol code	2305

Additional study identifiers

ISRCTN number	ISRCTN09599764
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	NHS Research Ethics Committee: 15/SC/0376

Notes:

Sponsors

Sponsor organisation name	University of Bristol
Sponsor organisation address	One Cathedral Square, Bristol, United Kingdom, BS1 5DD
Public contact	CEDAR Trial Manager (H Downing), University of Bristol, School of Social and Community Medicine, +44 01173313906, harriet.downing@bristol.ac.uk
Scientific contact	CEDAR Trial Manager (H Downing), University of Bristol, School of Social and Community Medicine, +44 01173313906, harriet.downing@bristol.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	01 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 November 2017
Global end of trial reached?	Yes
Global end of trial date	19 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of the CEDAR study is to investigate the clinical and cost effectiveness of benzocaine plus phenazone (active) ear drops compared to usual care (no drops) for reducing antibiotic consumption in children aged between twelve months and ten years presenting to primary care with AOM.

Protection of trial subjects:

Details of serious adverse events were collected, and the trial team notified immediately, using adverse event forms. Parents were also asked on the last day of their questionnaire whether their child had experienced any new or worsening symptoms during the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2016
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: 106
Worldwide total number of subjects	106
EEA total number of subjects	106

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)	14
Children (2-11 years)	92

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:

Due to a delay in the supply of a suitable placebo, recruitment began in October 2016, across 27 GP practices, randomising children to to the active treatment ("active drops") or usual care ("no drops"). When the placebo became available in March 2017 the 3-arm study began recruiting across 35 GP practices and recruitment ended in June 2017.

Pre-assignment

Screening details:

Combining figures from the 2- and 3-arm trials, 190 children (+ parents) were assessed for suitability. As 60 children were not invited to participate, e.g. clinician didn't have time, this left 130 children that were invited. 10 declined to participate, 10 were found to be ineligible and 4 were not recruited, resulting in 106 randomised children.

Period 1

Period 1 title	Baseline (5-arms)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Encompassing the 2-arm and 3-arm trials. The 2-arm trial was unblinded as both the clinician and parent/child were aware if they'd been allocated active drops or no treatment. The 3-arm trial was partially blinded as, if allocated to active or placebo drops, there was no way of distinguishing between the two. The PI and trial team remained blinded throughout the trial, apart from the trial statistician who was reporting to the data monitoring committee.

Arms

Are arms mutually exclusive?	Yes
Arm title	2-arm Active drops

Arm description:

The Investigational Medicinal Product (IMP) for this trial was a benzocaine and phenazone otic solution. This is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). For this trial we intended to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles.

Arm type	Active comparator
Investigational medicinal product name	Auralgan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution
Routes of administration	Auricular use

Dosage and administration details:

Parents were given instructions on how to administer the drops and asked to use them every 1 to 2 hours (up to a maximum of 12 times in 24 hours).

Arm title	2-arm No drops

Arm description:

No intervention.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	3-arm Active drops

Arm description:

The Investigational Medicinal Product (IMP) for this trial was a benzocaine and phenazone otic solution. This is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International

Nonproprietary Name, also known in the US as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). For this trial we intended to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles.

Arm type	Active comparator
Investigational medicinal product name	Auralgan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution
Routes of administration	Auricular use

Dosage and administration details:

Parents were given instructions on how to administer the drops and asked to use them every 1 to 2 hours (up to a maximum of 12 times in 24 hours).

Arm title	3-arm Placebo drops

Arm description:

The placebo was glycerine, with packaging as close in appearance as possible to that used for the active drops (Albany Molecular Research (Glasgow) Ltd).

Arm type	Placebo
Investigational medicinal product name	Placebo (one off production for the CEDAR trial by Albany Molecular Research (Glasgow) Ltd)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution
Routes of administration	Auricular use

Dosage and administration details:

Parents were given instructions on how to administer the drops and asked to use them every 1 to 2 hours (up to a maximum of 12 times in 24 hours).

Investigational medicinal product name	Placebo (one off production for the CEDAR trial by Albany Molecular Research (Glasgow) Ltd)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution
Routes of administration	Auricular use

Dosage and administration details:

Parents were given instructions on how to administer the drops and asked to use them every 1 to 2 hours (up to a maximum of 12 times in 24 hours).

Arm title	3-arm No drops

Arm description:

No intervention.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	2-arm Active drops	2-arm No drops	3-arm Active drops
Started	38	36	12
Completed	38	36	12

Number of subjects in period 1	3-arm Placebo drops	3-arm No drops
Started	10	10

Completed	10	10

Period 2

Period 2 title	2-arm trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Active drops

Arm description:

The Investigational Medicinal Product (IMP) for this trial was a benzocaine and phenazone otic solution. This is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). For this trial we intended to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles.

Arm type	Experimental
Investigational medicinal product name	Auralgan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution
Routes of administration	Auricular use

Dosage and administration details:

Parents were given instructions on how to administer the drops and asked to use them every 1 to 2 hours (up to a maximum of 12 times in 24 hours).

Arm title	No drops

Arm description:

No intervention.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2[1]	Active drops	No drops
Started	38	36
Completed	38	36

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Period 1 relates to all baseline data for the 2-arm and 3-arm trials. Period 2 then relates to the 2-arm trial only and period 3 relates to the 3-arm trial only. The number of individuals starting periods 2 and 3, added together, equal the number completing period 1.

Period 3

Period 3 title	3-arm trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Randomisation was stratified by centre in blocks of 30 packs, each block having the packs arranged in a random and consecutively numbered sequence. Each pack contained either 2 bottles of active medicine, 2 bottles of placebo medicine, or no bottles (a non-medicinal item of comparable weight). Patients were enrolled by their GP/nurse who were unaware of the contents of the next treatment pack in the sequence. When the trial pack was opened, those in the 'no drops' group became unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active drops

Arm description:

The Investigational Medicinal Product (IMP) for this trial was a benzocaine and phenazone otic solution. This is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). For this trial we intended to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles.

Arm type	Experimental
Investigational medicinal product name	Auralgan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution
Routes of administration	Auricular use

Dosage and administration details:

Parents were given instructions on how to administer the drops and asked to use them every 1 to 2 hours (up to a maximum of 12 times in 24 hours).

Arm title	No drops

Arm description:

No intervention.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo drops

Arm description:

The placebo was glycerine, with packaging as close in appearance as possible to that used for the active drops (Albany Molecular Research (Glasgow) Ltd).

Arm type	Placebo
Investigational medicinal product name	Placebo (one off production for the CEDAR trial by Albany Molecular Research (Glasgow) Ltd)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear drops, solution
Routes of administration	Auricular use

Dosage and administration details:

Parents were given instructions on how to administer the drops and asked to use them every 1 to 2 hours (up to a maximum of 12 times in 24 hours).

Number of subjects in period 3[2]	Active drops	No drops	Placebo drops
Started	12	10	10
Completed	12	10	10

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Period 1 relates to all baseline data for the 2-arm and 3-arm trials. Period 2 then relates to the 2-arm trial only and period 3 relates to the 3-arm trial only. The number of individuals starting periods 2 and 3, added together, equal the number completing period 1.

Baseline characteristics

Reporting groups	
Reporting group title	2-arm Active drops
Reporting group description:	
The Investigational Medicinal Product (IMP) for this trial was a benzocaine and phenazone otic solution. This is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). For this trial we intended to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles.	
Reporting group title	2-arm No drops
Reporting group description:	
No intervention.	
Reporting group title	3-arm Active drops
Reporting group description:	
The Investigational Medicinal Product (IMP) for this trial was a benzocaine and phenazone otic solution. This is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). For this trial we intended to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles.	
Reporting group title	3-arm Placebo drops
Reporting group description:	
The placebo was glycerine, with packaging as close in appearance as possible to that used for the active drops (Albany Molecular Research (Glasgow) Ltd).	
Reporting group title	3-arm No drops
Reporting group description:	
No intervention.	

Reporting group values	2-arm Active drops	2-arm No drops	3-arm Active drops
Number of subjects	38	36	12
Age categorical			
Age in years			
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)	7	4	2
Children (2-11 years)	31	32	10
Adolescents (12-17 years)	0	0	0
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	4.6	4.6	4.9
standard deviation	± 2.5	± 2.5	± 2.5

Gender categorical Units: Subjects			
Female	20	20	1
Male	18	16	11
Missing	0	0	0
Ethnic group Units: Subjects			
White	33	31	9
Other	1	0	1
Missing	4	5	2
Living in an area of deprivation			
Index of Multiple Deprivation based on the children's home postcode at birth, categorised as those living in the top 20% of deprived areas in the UK (England's 2015 rank and Wales' 2014 rank)			
Units: Subjects			
Yes	3	3	2
No	34	32	9
Missing	1	1	1
Smokers in household Units: Subjects			
Yes	2	1	1
No	32	30	9
Missing	4	5	2
Additional children in household Units: Subjects			
Yes	22	21	8
No	12	10	2
Missing	4	5	2
Breast fed at 3-months Units: Subjects			
Yes	14	9	7
No	20	22	3
Missing	4	5	2
Does the child wear a hearing aid Units: Subjects			
Yes	0	0	0
No	34	31	10
Missing	4	5	2
Flu vaccination during past 12 months Units: Subjects			
Yes	15	16	4
No	19	15	6
Missing	4	5	2
Mother attended with child Units: Subjects			
Yes	26	25	9
No	3	3	0
Missing	9	8	3
Accompanying adult employed/full time education/retired Units: Subjects			
Yes	25	26	7
No	9	5	3

Missing	4	5	2
Accompanying adult a university graduate Units: Subjects			
Yes	11	11	3
No	18	17	6
Missing	9	8	3
Received painkillers today			
Question: Has your child received any painkilling medicine, e.g. paracetamol or ibuprofen, in the last 6 hours before being checked for trial suitability			
Units: Subjects			
Yes	32	25	7
No	5	9	4
Missing	1	2	1
AOM in both ears (bilateral) Units: Subjects			
Yes	8	5	2
No	30	31	9
Missing	0	0	1
Given a delayed antibiotic Units: Subjects			
Yes	4	11	3
No	34	25	8
Missing	0	0	1
Accompanying adult's age Units: Years			
arithmetic mean	35.0	36.4	38.7
standard deviation	± 6.0	± 6.7	± 6.8
Child ear pain score (0-10)			
Answered by those aged >=5			
Units: Scale 0-10			
arithmetic mean	6.0	6.1	6.4
standard deviation	± 2.6	± 3.1	± 2.3
Parent ear pain score (0-10) Units: Scale 0-10			
arithmetic mean	6.9	6.3	6.3
standard deviation	± 1.5	± 1.7	± 1.8
Number of days in pain Units: Days			
arithmetic mean	2.7	2.5	1.5
standard deviation	± 2.0	± 1.4	± 0.9
Episodes of distress/crying (0-6) Units: 0-6			
arithmetic mean	3.8	3.3	3.0
standard deviation	± 1.5	± 1.3	± 1.7
Disturbed sleep (0-6) Units: 0-6			
arithmetic mean	4.1	3.7	2.9
standard deviation	± 1.6	± 1.6	± 1.5
Interference with normal activities (0-6) Units: 0-6			
arithmetic mean	3.1	2.7	2.5

standard deviation	± 1.5	± 1.5	± 1.8
Eating/drinking less than normal (0-6)			
Units: 0-6			
arithmetic mean	2.7	2.2	1.7
standard deviation	± 1.7	± 1.6	± 1.6
Fever (0-6)			
Units: 0-6			
arithmetic mean	1.9	2.7	1.2
standard deviation	± 1.7	± 1.7	± 1.6
Hearing problems (0-6)			
Units: 0-6			
arithmetic mean	1.2	1.4	1.4
standard deviation	± 1.4	± 1.8	± 1.6
Cough (0-6)			
Units: 0-6			
arithmetic mean	2.5	1.8	1.0
standard deviation	± 1.8	± 1.7	± 1.0
Blocked/runny nose (0-6)			
Units: 0-6			
arithmetic mean	2.3	2.1	1.8
standard deviation	± 1.8	± 1.8	± 1.9
Vomiting (0-6)			
Units: 0-6			
arithmetic mean	0.5	0.4	0.2
standard deviation	± 1.5	± 1.0	± 0.6
General health (0-10)			
From 0 (not at all unwell) to 10 (extremely unwell)			
Units: 0-10			
arithmetic mean	3.6	3.3	3.9
standard deviation	± 1.9	± 1.8	± 1.7
Temperature			
Units: Degrees celsius			
arithmetic mean	37.0	36.9	37.1
standard deviation	± 0.6	± 0.7	± 0.8

Reporting group values	3-arm Placebo drops	3-arm No drops	Total
Number of subjects	10	10	106
Age categorical			
Age in years			
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	1	14
Children (2-11 years)	10	9	92
Adolescents (12-17 years)	0	0	0
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	5.0	4.6	
standard deviation	± 1.9	± 2.9	-
Gender categorical Units: Subjects			
Female	7	5	53
Male	3	5	53
Missing	0	0	0
Ethnic group Units: Subjects			
White	6	9	88
Other	1	0	3
Missing	3	1	15
Living in an area of deprivation			
Index of Multiple Deprivation based on the children's home postcode at birth, categorised as those living in the top 20% of deprived areas in the UK (England's 2015 rank and Wales' 2014 rank)			
Units: Subjects			
Yes	0	4	12
No	10	6	91
Missing	0	0	3
Smokers in household Units: Subjects			
Yes	1	2	7
No	6	7	84
Missing	3	1	15
Additional children in household Units: Subjects			
Yes	4	7	62
No	3	2	29
Missing	3	1	15
Breast fed at 3-months Units: Subjects			
Yes	4	2	36
No	3	7	55
Missing	3	1	15
Does the child wear a hearing aid Units: Subjects			
Yes	0	0	0
No	7	9	91
Missing	3	1	15
Flu vaccination during past 12 months Units: Subjects			
Yes	4	4	43
No	3	5	48
Missing	3	1	15
Mother attended with child Units: Subjects			
Yes	5	8	73
No	2	0	8
Missing	3	2	25

Accompanying adult employed/full time education/retired Units: Subjects			
Yes	6	3	67
No	1	6	24
Missing	3	1	15
Accompanying adult a university graduate Units: Subjects			
Yes	3	3	31
No	4	4	49
Missing	3	3	26
Received painkillers today			
Question: Has your child received any painkilling medicine, e.g. paracetamol or ibuprofen, in the last 6 hours before being checked for trial suitability			
Units: Subjects			
Yes	4	7	75
No	5	3	26
Missing	1	0	5
AOM in both ears (bilateral) Units: Subjects			
Yes	4	2	21
No	6	8	84
Missing	0	0	1
Given a delayed antibiotic Units: Subjects			
Yes	1	3	22
No	9	7	83
Missing	0	0	1
Accompanying adult's age Units: Years			
arithmetic mean	37.6	31.5	
standard deviation	± 8.2	± 3.1	-
Child ear pain score (0-10)			
Answered by those aged >=5			
Units: Scale 0-10			
arithmetic mean	5.5	7.5	
standard deviation	± 3.0	± 2.5	-
Parent ear pain score (0-10) Units: Scale 0-10			
arithmetic mean	5.3	6.2	
standard deviation	± 1.3	± 2.2	-
Number of days in pain Units: Days			
arithmetic mean	2.7	2.3	
standard deviation	± 1.5	± 1.8	-
Episodes of distress/crying (0-6) Units: 0-6			
arithmetic mean	2.4	4.2	
standard deviation	± 1.3	± 1.7	-
Disturbed sleep (0-6) Units: 0-6			

arithmetic mean	2.7	4.2	
standard deviation	± 1.3	± 1.3	-
Interference with normal activities (0-6)			
Units: 0-6			
arithmetic mean	2.9	3.3	
standard deviation	± 1.5	± 1.3	-
Eating/drinking less than normal (0-6)			
Units: 0-6			
arithmetic mean	2.4	2.0	
standard deviation	± 1.8	± 1.7	-
Fever (0-6)			
Units: 0-6			
arithmetic mean	2.1	2.1	
standard deviation	± 1.5	± 1.9	-
Hearing problems (0-6)			
Units: 0-6			
arithmetic mean	1.0	0.7	
standard deviation	± 1.6	± 1.1	-
Cough (0-6)			
Units: 0-6			
arithmetic mean	2.2	1.5	
standard deviation	± 1.7	± 1.6	-
Blocked/runny nose (0-6)			
Units: 0-6			
arithmetic mean	1.7	2.9	
standard deviation	± 1.1	± 1.8	-
Vomiting (0-6)			
Units: 0-6			
arithmetic mean	0.4	0.5	
standard deviation	± 1.3	± 1.1	-
General health (0-10)			
From 0 (not at all unwell) to 10 (extremely unwell)			
Units: 0-10			
arithmetic mean	3.3	3.1	
standard deviation	± 1.5	± 1.2	-
Temperature			
Units: Degrees celsius			
arithmetic mean	37.5	37.1	
standard deviation	± 1.3	± 0.6	-

End points

End points reporting groups

Reporting group title	2-arm Active drops

Reporting group description:

The Investigational Medicinal Product (IMP) for this trial was a benzocaine and phenazone otic solution. This is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). For this trial we intended to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles.

Reporting group title	2-arm No drops

Reporting group description:

No intervention.

Reporting group title	3-arm Active drops

Reporting group description:

The Investigational Medicinal Product (IMP) for this trial was a benzocaine and phenazone otic solution. This is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). For this trial we intended to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles.

Reporting group title	3-arm Placebo drops

Reporting group description:

The placebo was glycerine, with packaging as close in appearance as possible to that used for the active drops (Albany Molecular Research (Glasgow) Ltd).

Reporting group title	3-arm No drops

Reporting group description:

No intervention.

Reporting group title	Active drops

Reporting group description:

The Investigational Medicinal Product (IMP) for this trial was a benzocaine and phenazone otic solution. This is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). For this trial we intended to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles.

Reporting group title	No drops

Reporting group description:

No intervention.

Reporting group title	Active drops

Reporting group description:

The Investigational Medicinal Product (IMP) for this trial was a benzocaine and phenazone otic solution. This is an oil based, combined local anaesthetic (benzocaine) and analgesic (phenazone, International Nonproprietary Name, also known in the US as antipyrine) ear drop. One millilitre contains 14 mg (1.4%) of benzocaine and 54mg (5.4%) phenazone suspended in a glycerine-based liquid along with a preservative (hydroxyquinolone sulphate). For this trial we intended to test Auralgan©, manufactured by Pfizer Consumer Healthcare (Australia) and sold in 15mL bottles.

Reporting group title	No drops

Reporting group description:

No intervention.

Reporting group title	Placebo drops

Reporting group description:

The placebo was glycerine, with packaging as close in appearance as possible to that used for the active drops (Albany Molecular Research (Glasgow) Ltd).

Primary: Antibiotic consumption (Active vs. No drops)	
End point title	Antibiotic consumption (Active vs. No drops)
End point description:	
Question: Did your child consume antibiotics by mouth today? Y/N	
End point type	Primary
End point timeframe:	
Asked whether or not the child had taken antibiotics every day for 8 days.	

End point values	Active drops	No drops	Active drops	No drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	29	30	10	8
Units: Yes or No to consumption during the week				
Yes	1	9	0	2
No	28	21	10	6

End point values	Placebo drops			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Yes or No to consumption during the week				
Yes	3			
No	4			

Statistical analyses

Statistical analysis title	Odds Ratio (Active vs. No drops)
Statistical analysis description:	
When comparing active and no drops arms in the 2-arm trial, logistic regression was employed, with and without adjustment. When comparing active and no drops in the 3-arm trial the calculations were made by hand, using a continuity correction of 0.4444 to account for the zero numerator. The results were then combined in a meta-analysis (using the inverse method) to give an overall comparison between arms.	
Comparison groups	Active drops v No drops v Active drops v No drops
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.55
Variability estimate	Standard error of the mean

Notes:

[1] - Unadjusted p value = 0.009 whereas adjustment for delayed antibiotic script was 0.035.

Secondary: Ear Pain on Day 2 (Active vs. Placebo; No drops vs. Placebo; Active vs. No drops))

End point title	Ear Pain on Day 2 (Active vs. Placebo; No drops vs. Placebo; Active vs. No drops))

End point description:

Question: Please score your overall impression of your child's ear pain over the last 24 hours using the scale and write the score in the boxes below. Scale 0 (no pain) to 10 (worst possible pain).

End point type	Secondary

End point timeframe:

Parents were asked to rate their child's pain on a scale of 0 to 10 every day for 8 days. This measurement was taken on the evening of Day 2.

End point values	Active drops	No drops	Active drops	No drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	30	10	9
Units: Pain: 0 (no pain) to 10 (worst possible)				
arithmetic mean (standard deviation)	2.81 (± 2.32)	4.43 (± 2.54)	3.10 (± 2.23)	5.00 (± 1.73)

End point values	Placebo drops			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Pain: 0 (no pain) to 10 (worst possible)				
arithmetic mean (standard deviation)	2.14 (± 1.07)			

Statistical analyses

Statistical analysis title	Difference in means (Active vs. placebo)

Statistical analysis description:

Difference in mean ear pain between the active drops group and placebo drops group, with additional adjustment for parent reported pain score at consultation.

Comparison groups	Active drops v Placebo drops

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.312 [2]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.99
upper limit	2.91
Variability estimate	Standard error of the mean

Notes:

[2] - Unadjusted p value = 0.312, Adjusting for parent reported pain score at consultation = 0.506.

Statistical analysis title	Difference in means (No drops vs. placebo)

Statistical analysis description:

Difference in mean ear pain between the no drops group and placebo drops group, with additional adjustment for parent reported pain score at consultation.

Comparison groups	No drops v Placebo drops
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [3]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	2.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.25
upper limit	4.46
Variability estimate	Standard error of the mean

Notes:

[3] - Unadjusted p value = 0.002. Adjusting for parent reported pain score at consultation = 0.003.

Statistical analysis title	Difference in means (Active vs. no drops)

Statistical analysis description:

As an exploratory analysis, the active and no drops groups were compared separately in the 2-arm and 3-arm trials to establish whether there was a difference in ear pain between the two groups. The results were pooled using the inverse variance meta-analysis method.

Comparison groups	Active drops v No drops v Active drops v No drops
Number of subjects included in analysis	81
Analysis specification	Post-hoc
Analysis type	superiority[4]
P-value	= 0.001 [5]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.74
upper limit	-0.66
Variability estimate	Standard error of the mean

Notes:

[4] - Exploratory

[5] - Unadjusted p=0.001, Adjusting for parent reported pain score at consultation <0.001.

Secondary: Ear Pain on Day 1 (Active vs. Placebo)

End point title	Ear Pain on Day 1 (Active vs. Placebo)

End point description:

Question: Please score your child's ear pain as close to 1 hour (60 minutes) after giving the ear drops as possible, using the scale and write the score in the boxes below. Scale 0 (no pain) to 10 (worst possible pain).

End point type	Secondary

End point timeframe:

Parents were asked to rate their child's pain on a scale of 0 to 10 every day for 8 days. This measurement was taken approximately one hour after administering the drops in the consultation (Day 1).

End point values	Active drops	Placebo drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	7		
Units: Pain: 0 (no pain) to 10 (worst possible)				
arithmetic mean (standard deviation)	2.70 (± 1.16)	3.42 (± 1.62)		

Statistical analyses

Statistical analysis title	Difference in means (Active vs. placebo)

Statistical analysis description:

Difference in mean ear pain on Day 1 between active and placebo groups, presenting unadjusted results as well as after adjusting for parent reported pain score at consultation.

Comparison groups	Active drops v Placebo drops
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.295 [6]
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.16
upper limit	0.7

Variability estimate	Standard error of the mean

Notes:

[6] - Unadjusted p = 0.295. Adjusted for parent reported ear pain at consultation = 0.338.

Secondary: Analgesic consumption (Active vs. Placebo)

End point title	Analgesic consumption (Active vs. Placebo)

End point description:

Parents answered Y or N and these answers were compiled to create an overall Y/N binary consumption variable.

End point type	Secondary

End point timeframe:

Parents were asked everyday for 8 days whether their child had consumed ibuprofen, paracetamol or other pain-killing remedies during the day.

End point values	Active drops	Placebo drops		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	7		
Units: Consumption of analgesics (Y/N)				
Yes	8	6		
No	1	1		

Statistical analyses

Statistical analysis title	Odds Ratio (Active vs. placebo)

Statistical analysis description:

Logistic regression to compare analgesic consumption between active and placebo groups. Unadjusted results were presented, as well as results after adjustment for parent reported pain score at consultation.

Comparison groups	Active drops v Placebo drops
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.849 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	25.91
Variability estimate	Standard error of the mean

Notes:

[7] - Unadjusted p=0.849. Adjustment for parent reported pain score at consultation = 0.911

Secondary: Overall Symptom Burden (No drops vs. Active; Placebo vs. Active)

End point title	Overall Symptom Burden (No drops vs. Active; Placebo vs. Active)

End point description:

Thinking about and comparing your child's normal behaviour when well, did he/she have any of the following symptoms over the last 24 hours? Episodes of distress/crying (0-6), Disturbed sleep (0-6), Interference with normal activities (0-6), Eating or drinking less than normal (0-6), High temperature/fever (0-6), Hearing problems (0-6). Where 0 is "normal" and 6 is "extremely bad".

End point type	Secondary

End point timeframe:

Overall symptom burden over 8 days, where each day consisted of 6 questions on a scale of 0 to 6. Therefore the area under the curve could be between 0 (0 for eight days) and 288 (6*6 for 8 days).

End point values	Active drops	No drops	Active drops	No drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	28	10	9
Units: Area under the curve				
median (inter-quartile range (Q1-Q3))	11.5 (5.8 to 33.5)	30.3 (6.3 to 45.0)	15.8 (8.5 to 21.5)	28.5 (14.0 to 42.0)

End point values	Placebo drops			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Area under the curve				
median (inter-quartile range (Q1-Q3))	24.5 (10.5 to 50.5)			

Statistical analyses

Statistical analysis title	Difference in means (No drops vs. active, 2-arm)

Statistical analysis description:

Comparison in mean (square root) area under the curves for the active and no drops groups (in the 2-arm trial). Due to the skewed nature we compared the square root AUC.

Comparison groups	Active drops v No drops
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.094
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	2.49

Variability estimate	Standard error of the mean

Statistical analysis title	Difference in means (No drops vs. active, 3-arm)
Statistical analysis description:	
Comparison in mean (square root) area under the curves for the active and no drops groups (in the 3-arm trial). Due to the skewed nature we compared the square root AUC.	
Comparison groups	Active drops v No drops
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.072
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	2.84
Variability estimate	Standard error of the mean

Statistical analysis title	Difference in means (Placebo vs. active, 3-arm)
Statistical analysis description:	
Comparison in mean (square root) area under the curves for the active and placebo groups (in the 2-arm trial). Due to the skewed nature we compared the square root AUC.	
Comparison groups	Placebo drops v Active drops
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.085
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	3.9
Variability estimate	Standard error of the mean

Secondary: Overall illness duration (Placebo vs. Active; No drops vs. Active)	
End point title	Overall illness duration (Placebo vs. Active; No drops vs. Active)
End point description:	
The number of days until the parent rated score of pain is zero for 2 consecutive days.	

End point type	Secondary
End point timeframe: 8 days	

End point values	Active drops	No drops	Active drops	No drops
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	34	31	10	9
Units: Pain duration (days)				
median (inter-quartile range (Q1-Q3))	3 (2 to 5)	4 (3 to 999)	3 (3 to 5)	3 (2 to 6)

End point values	Placebo drops			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Pain duration (days)				
median (inter-quartile range (Q1-Q3))	2 (2 to 4)			

Statistical analyses

Statistical analysis title	Hazard ratio (No drops vs. Active 2-arm)
Statistical analysis description: Time to event (Kaplan Meier) where the event is two consecutive days of 0 pain (recovery).	
Comparison groups	No drops v Active drops
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.11
Variability estimate	Standard error of the mean

Statistical analysis title	Hazard ratio (No drops vs. Active 3-arm)
Statistical analysis description: Time to event (Kaplan Meier) where the event is two consecutive days of 0 pain (recovery).	
Comparison groups	No drops v Active drops

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	2.61
Variability estimate	Standard error of the mean

Statistical analysis title	Hazard ratio (Placebo vs. Active)
Statistical analysis description:	
Time to event (Kaplan Meier) where the event is two consecutive days of 0 pain (recovery).	
Comparison groups	Placebo drops v Active drops
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	4.75
Variability estimate	Standard error of the mean

Secondary: Parent satisfaction

End point title	Parent satisfaction
End point description:	
Valid only for active and placebo drop group children (and respective parents). Parents were asked: Overall how satisfied were you with the trial ear drops your child received for their ear pain? Satisfied; neither satisfied nor disatisfied; not satisfied.	
End point type	Secondary
End point timeframe:	
At the end of the week, on day 8, parents were asked if they were satisfied with the drops	

End point values	Active drops	Active drops	Placebo drops	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	10	7	
Units: Categorical				
Satisfied	27	9	4	
Neither satisfied nor disatisfied	2	1	2	
Not satisfied	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At the end of the trial (8 days after randomisation) parents were asked to report any new or worsening symptoms.

Adverse event reporting additional description:

We were alerted to any serious adverse events by the site principal investigator. All other adverse events were captured within the parental questionnaire. All non-serious adverse events were categorised as mild, moderate or severe.

Assessment type	Systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	1.36.4

Reporting groups

Reporting group title	Active drops
Reporting group description: -	
Reporting group title	Placebo drops
Reporting group description: -	
Reporting group title	No drops

Reporting group description: -

Serious adverse events	Active drops	Placebo drops	No drops
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	0 / 10 (0.00%)	1 / 46 (2.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Respiratory, thoracic and mediastinal disorders			
Difficulty breathing	Additional description: Child admitted to hospital due to breathing issues. The child was discharged from the hospital the next day and the parent completed the questionnaire. This child was allocated to the usual care group, and so the event is unrelated to treatment.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 10 (0.00%)	1 / 46 (2.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0.5 %

Non-serious adverse events	Active drops	Placebo drops	No drops
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 50 (4.00%)	0 / 10 (0.00%)	4 / 46 (8.70%)
Nervous system disorders			

Problem with balance	Additional description: Reported as moderate.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 10 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ringing in ear	Additional description: Reported as mild.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 10 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Common cold	Additional description: Reported as moderate.		
subjects affected / exposed	1 / 50 (2.00%)	0 / 10 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0
Bleeding from nose	Additional description: Reported as moderate.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 10 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Itching of skin	Additional description: Reported as moderate. They reported itching around the neck.		
subjects affected / exposed	0 / 50 (0.00%)	0 / 10 (0.00%)	1 / 46 (2.17%)
occurrences (all)	0	0	1
Infections and infestations			
Chicken pox	Additional description: Reported as mild.		
subjects affected / exposed	1 / 50 (2.00%)	0 / 10 (0.00%)	0 / 46 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 September 2017	The project start date was 1st January 2015, and the planned study end date was 31st March 2018. Issues were encountered with a lengthy delay to the IMP supply. While the IMP supplier was identified through a competitive procurement process, the supplier failed to deliver the active drops and placebo in line with expected and revised timeframes. The trial team requested a variation to the contract with the funder to allow for the trial to reach its target. On the 1st of September 2017, the funder declined the contract variation and requested for the trial to be closed down. The project closed early, on 31st December 2017, as required by the funders.	-

Notes:

Limitations and caveats

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

The project closed early, on 31st December 2017, as required by the funders. Analyses were based on a limited sample size therefore results should be viewed with caution. Some analyses were not conducted owing to low numbers.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31304912