



## Clinical trial results:

**A randomised controlled trial to measure the effects and costs of a dental caries prevention regime for young children attending primary care dental services.**

### Summary

EudraCT number	2009-010725-39
Trial protocol	GB
Global end of trial date	22 June 2015

### Results information

Result version number	v1 (current)
This version publication date	03 March 2018
First version publication date	03 March 2018

### Trial information

#### Trial identification

Sponsor protocol code	08/14/19
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#### Additional study identifiers

ISRCTN number	ISRCTN36180119
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Belfast Health and Social Care Trust
Sponsor organisation address	A Floor, Belfast City Hospital, Lisburn Road, Belfast, United Kingdom, BT9 7AB
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Scientific contact	Professor Martin Tickle, University of Manchester, +44(0) 1612756610, martin.tickle@manchester.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	28 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2015
Global end of trial reached?	Yes
Global end of trial date	22 June 2015
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To compare over a 3 year period the effectiveness of 22,600 ppm fluoride varnish, 1,450 ppm fluoride toothpaste, toothbrush and standardised health education, provided twice a year, as a preventive package, with standardised health education alone provided twice a year in:

- preventing the conversion of children from caries-free to caries-active states in the primary dentition
- reducing the number of carious surfaces (caries into dentine) in the primary dentition in children who convert from caries free to caries active states
- preventing episodes of pain and extraction of primary teeth in 2 and 3 year-old children who are caries free at baseline and who attend primary care dental services.

To compare over a 3 year period the costs of dental care in the group receiving 22,600 ppm fluoride varnish, 1,450 ppm fluoride toothpaste, toothbrush and standardised health education, provided twice a year as a preventive package, with the group receiving standardised health education alone.

Protection of trial subjects:

The risks for children in the intervention group included allergic responses to the varnish, therefore children who had been hospitalised due to allergic reactions were excluded from the trial. There was also a risk of children in the intervention group developing fluorosis, however this risk was unlikely as the varnish was professionally applied and standardised advice on the safe use of toothpaste was given to all participants. An independent data monitoring and ethics committee was also convened for the trial.

Background therapy:

Not Applicable

Evidence for comparator:

The comparator was standardised health education advice.

Actual start date of recruitment	12 April 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: 1248
Worldwide total number of subjects	1248
EEA total number of subjects	1248

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)	1248
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:

Recruitment took place between 12/04/2011 and 29/06/2012 from 22 general dental practices in Northern Ireland. 1248 children aged 2-3 years and who were caries free were recruited into the trial, exceeding the planned sample size of 1200.

### Pre-assignment

Screening details:

A total of 2455 were screened by Community Dental Service dentists according to the trial inclusion/exclusion criteria. Children were excluded if they had a past history of fillings or extractions due to caries, fissure sealants on primary molar teeth, a history of severe allergic reactions requiring hospitalization or participating in an IMP study

### Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor <sup>[1]</sup>

Blinding implementation details:

The study was a two-arm, parallel-group, randomised controlled trial, with an allocation ratio of 1 : 1. Randomisation was undertaken by the clinical trials unit using randomised permuted blocks. Children/parents and general dental practice staff were not blinded; however, the Community Dental Service dentists who completed the outcome assessment were blinded to treatment allocation.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Intervention

Arm description:

The intervention was composite in nature, comprising a varnish containing 22,600 parts per million (p.p.m.) fluoride, a toothbrush and a 50-ml tube of toothpaste containing 1450 p.p.m. fluoride; plus standardised, evidence-based prevention advice provided at 6-monthly intervals over 3 years.

Arm type	Experimental
Investigational medicinal product name	Duraphat
Investigational medicinal product code	PL 00049/0042
Other name	
Pharmaceutical forms	Dental suspension
Routes of administration	Dental use

Dosage and administration details:

22,600 ppm of fluoride varnish was applied to the dried primary teeth of the children by a participating dentist following the product brochure, and a fluoride varnish application protocol which described the process of application for participating dentists. Up to 0.25 ml (=5.65 mg Fluoride) was applied twice a year at each 6 month visit and in total children would have received a maximum of 6 applications over the duration of the trial.

<b>Arm title</b>	Control
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Arm description:

The control group received standardised health education advice alone at 6-monthly intervals over 3 years.

Arm type	Advice Only
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No investigational medicinal product assigned in this arm

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Children, parents and the general dental practice staff were not blinded. However the Community Dental staff who completed the outcome assessment were blinded to treatment allocation.

<b>Number of subjects in period 1</b>	Intervention	Control
Started	624	624
Completed	549	547
Not completed	75	77
Subject completed but no data chart available	1	-
Lost to follow-up	74	77

## Baseline characteristics

### Reporting groups

Reporting group title	Intervention
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Reporting group description:

The intervention was composite in nature, comprising a varnish containing 22,600 parts per million (p.p.m.) fluoride, a toothbrush and a 50-ml tube of toothpaste containing 1450 p.p.m. fluoride; plus standardised, evidence-based prevention advice provided at 6-monthly intervals over 3 years.

Reporting group title	Control
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Reporting group description:

The control group received standardised health education advice alone at 6-monthly intervals over 3 years.

Reporting group values	Intervention	Control	Total
Number of subjects	624	624	1248
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	624	624	1248
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	3.1	3.1	
standard deviation	± 0.53	± 0.53	-
Gender categorical			
Units: Subjects			
Female	341	328	669
Male	283	296	579
Socioeconomic Status - MDM 2010			
Units: Subjects			
Quintile 1 (most deprived)	88	106	194
Quintile 2	141	134	275
Quintile 3	172	155	327
Quintile 4	148	155	303
Quintile 5 (least deprived)	74	73	147
Missing	1	1	2

## End points

### End points reporting groups

Reporting group title	Intervention
Reporting group description: The intervention was composite in nature, comprising a varnish containing 22,600 parts per million (p.p.m.) fluoride, a toothbrush and a 50-ml tube of toothpaste containing 1450 p.p.m. fluoride; plus standardised, evidence-based prevention advice provided at 6-monthly intervals over 3 years.	
Reporting group title	Control
Reporting group description: The control group received standardised health education advice alone at 6-monthly intervals over 3 years.	

### Primary: Conversion from caries free to caries active

End point title	Conversion from caries free to caries active
End point description: The primary outcome, the number (percentage) of children who converted to caries active over the trial.	
End point type	Primary
End point timeframe: 3 years	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	547		
Units: Subjects	187	213		

### Statistical analyses

Statistical analysis title	Conversion of caries free to caries active
Statistical analysis description: A logistic regression model was fitted adjusting for age and socioeconomic status measured by MDM 2010 quintiles.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	1096
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.11
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.04
Variability estimate	Standard error of the mean
Dispersion value	0.1

## Secondary: Number of decayed, missing, filled tooth surfaces in caries active children

End point title	Number of decayed, missing, filled tooth surfaces in caries active children
End point description: The number of decayed, missing, filled tooth surfaces was calculated for each child, who were caries active.	
End point type	Secondary
End point timeframe: 3 years	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187 <sup>[1]</sup>	213 <sup>[2]</sup>		
Units: carious surfaces				
arithmetic mean (standard deviation)	7.18 (± 7.99)	9.61 (± 8.75)		

Notes:

[1] - Caries active children

[2] - Caries active children

## Statistical analyses

Statistical analysis title	Decayed, missing filled tooth surfaces
Statistical analysis description: A multiple linear regression analysis adjusted for age and socioeconomic status measured by MDM 2010 quintiles.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.007
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.96
upper limit	-0.63



Variability estimate	Standard error of the mean
Dispersion value	0.85

### Secondary: Number of extracted teeth in caries active children

End point title	Number of extracted teeth in caries active children
End point description: The number of extracted teeth was calculated for each child who was caries active.	
End point type	Secondary
End point timeframe: 3 years	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187 <sup>[3]</sup>	213 <sup>[4]</sup>		
Units: Teeth				
arithmetic mean (standard deviation)	0.45 (± 1.43)	0.46 (± 1.44)		

Notes:

[3] - Caries active children

[4] - Caries active children

### Statistical analyses

<b>Statistical analysis title</b>	Number of extracted teeth
Statistical analysis description: A negative binomial model was fitted for the number of extracted teeth, which indicated significant overdispersion and was not statistically significant. A post hoc analysis on the number of children who had teeth extracted was undertaken for the children who were caries active.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.95
Method	Negative binomial regression
Parameter estimate	Negative binomial regression coefficient
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.82
Variability estimate	Standard error of the mean
Dispersion value	0.43

### Secondary: Number of caries active children with extracted teeth

End point title	Number of caries active children with extracted teeth
End point description: Number of caries active children with teeth extracted.	
End point type	Secondary
End point timeframe: 3 years	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187 <sup>[5]</sup>	213 <sup>[6]</sup>		
Units: Subjects	21	28		

Notes:

[5] - Caries active children

[6] - Caries active children

### Statistical analyses

<b>Statistical analysis title</b>	Number of children with teeth extracted
Statistical analysis description: The planned negative binomial regression model indicated overdispersion. A logistic regression model was fitted adjusting for age and socioeconomic status measured by MDM 2010 quintiles.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	400
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.56
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.54
Variability estimate	Standard error of the mean
Dispersion value	0.26

### Secondary: Number of episodes of pain

End point title	Number of episodes of pain
End point description: Number of episodes of pain for all children.	
End point type	Secondary
End point timeframe: 3 years	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549 <sup>[7]</sup>	547 <sup>[8]</sup>		
Units: Episode of pain				
arithmetic mean (standard deviation)	0.37 (± 0.95)	0.47 (± 1.14)		

Notes:

[7] - All children

[8] - All children

## Statistical analyses

Statistical analysis title	Number of episodes of pain
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Statistical analysis description:

A negative binomial regression model was fitted adjusting for caries status, age and socioeconomic status measured by MDM 2010 quintiles. There was significant overdispersion and this was not statistically significant. A post hoc analysis on the number of children having pain was also undertaken.

Comparison groups	Intervention v Control
Number of subjects included in analysis	1096
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.81
Method	negative binomial regression
Parameter estimate	negative binomial regression coefficient
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.15

## Secondary: Number of children who had pain

End point title	Number of children who had pain
End point description:	
Number of children who had pain.	
End point type	Secondary
End point timeframe:	
3 years	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549 <sup>[9]</sup>	547 <sup>[10]</sup>		
Units: Subjects	106	120		

Notes:

[9] - All children

[10] - All children

## Statistical analyses

Statistical analysis title	Number of children who had pain
Statistical analysis description:	
A logistic regression adjusted for caries status, age and socioeconomic status measured by MDM 2010 quintiles was undertaken for the number of children with pain.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	1096
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.74
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	0.15

## Secondary: Number of serious adverse events

End point title	Number of serious adverse events
End point description:	
Number of serious adverse events in all children, over 3 years.	
End point type	Secondary
End point timeframe:	
Over 3 years	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	624 <sup>[11]</sup>	624 <sup>[12]</sup>		
Units: Serious Adverse Events				
arithmetic mean (standard deviation)	0.09 (± 0.34)	0.072 (± 0.31)		

Notes:

[11] - All children randomised

**Statistical analyses**

<b>Statistical analysis title</b>	Number of Serious Adverse Events
Statistical analysis description:	
A negative binomial analysis was fitted, adjusting for age and socioeconomic status measured by MDM 2010 quintiles. There was significant overdispersion and a logistic regression model was fitted post hoc for whether a child had a SAE or not.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	1248
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.42
Method	Negative binomial regression
Parameter estimate	Negative binomial regression coefficient
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.65
Variability estimate	Standard error of the mean
Dispersion value	0.24

**Secondary: Number of children having serious adverse events**

End point title	Number of children having serious adverse events
End point description:	
Number of children randomized having a serious adverse event over 3 years.	
End point type	Secondary
End point timeframe:	
Over 3 years	

<b>End point values</b>	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	624 <sup>[13]</sup>	624 <sup>[14]</sup>		
Units: Subjects	45	37		

Notes:

[13] - All children randomised

[14] - All children randomised

**Statistical analyses**

<b>Statistical analysis title</b>	Number of children who had SAEs
Statistical analysis description: A logistic regression model was fitted, adjusting for age and socioeconomic status measured by MDM 2010 quintiles. This was not statistically significant.	
Comparison groups	Intervention v Control
Number of subjects included in analysis	1248
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.36
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.94
Variability estimate	Standard error of the mean
Dispersion value	0.28

## Secondary: Mean difference health service cost/mean difference in proportion caries free

End point title	Mean difference health service cost/mean difference in proportion caries free
End point description: Incremental cost-effectiveness as difference in health service costs divided by the proportion caries free intervention vs control.	
End point type	Secondary
End point timeframe: 3 Years	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	547		
Units: Cost per proportion caries free				
arithmetic mean (confidence interval 95%)	-2092.59 (-30100.4 to 27921.8)	-2092.59 (-30100.4 to 27921.8)		

## Statistical analyses

<b>Statistical analysis title</b>	Incremental cost-effectiveness
Statistical analysis description: Incremental cost-effectiveness. A sampling distribution for the incremental cost-effectiveness ratio was simulated based on a bootstrapped sample. The 2.5 and 97.5 percentiles for the ratio were used to	

establish the 95% confidence interval for the distribution.

Comparison groups	Intervention v Control
Number of subjects included in analysis	1096
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Incremental cost-effectiveness ratio
Parameter estimate	Incremental cost-effectiveness ratio
Point estimate	-2092.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30100.4
upper limit	27921.8

## Secondary: Mean difference in health service cost/mean difference in number of carious surfaces

End point title	Mean difference in health service cost/mean difference in number of carious surfaces
End point description: Incremental cost-effectiveness as difference in health service costs divided by the number of carious surfaces intervention vs control.	
End point type	Secondary
End point timeframe: 3 Years	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	547		
Units: Cost per number of carious surfaces				
arithmetic mean (confidence interval 95%)	-250.58 (-454.39 to -79.52)	-250.58 (-454.39 to -79.52)		

## Statistical analyses

Statistical analysis title	Incremental cost-effectiveness
Statistical analysis description: Incremental cost-effectiveness. A sampling distribution for the incremental cost-effectiveness ratio was simulated based on a bootstrapped sample. The 2.5 and 97.5 percentiles for the ratio were used to establish the 95% confidence interval for the distribution.	
Comparison groups	Intervention v Control

Number of subjects included in analysis	1096
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Incremental cost effectiveness ratio
Parameter estimate	Incremental cost effectiveness ratio
Point estimate	-250.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-454.39
upper limit	-79.52

### Secondary: Mean difference in health service cost/mean difference in number of episodes of pain

End point title	Mean difference in health service cost/mean difference in number of episodes of pain
End point description: Incremental cost-effectiveness as difference in health service costs divided by the number of episodes of pain intervention vs control.	
End point type	Secondary
End point timeframe: 3 Years	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	549	547		
Units: Cost per number of carious surfaces				
arithmetic mean (confidence interval 95%)	-259.07 (-14644 to 14941.60)	-259.07 (-14644 to 14941.60)		

### Statistical analyses

Statistical analysis title	Incremental cost-effectiveness
Statistical analysis description: Incremental cost-effectiveness. A sampling distribution for the incremental cost-effectiveness ratio was simulated based on a bootstrapped sample. The 2.5 and 97.5 percentiles for the ratio were used to establish the 95% confidence interval for the distribution.	
Comparison groups	Intervention v Control



Number of subjects included in analysis	1096
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.05
Method	Incremental cost-effectiveness ratio
Parameter estimate	Incremental cost-effectiveness ratio
Point estimate	-259.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14664
upper limit	14941.6

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The adverse event (AE) reporting period for the trial began upon enrolment in to the study and ended at the 36 month visit. All SAEs were to be reported to the clinical trials unit within 24 hours of the local investigator becoming aware of the event.

Adverse event reporting additional description:

All adverse events (AEs) were recorded and once causality was determined only adverse reactions (ARs) and SAEs were reported to the clinical trials unit. Due to small numbers a breakdown of term is not provided for serious and non-serious AEs.

Assessment type	Systematic
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### Dictionary used

Dictionary name	NICTC
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Dictionary version	4
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### Reporting groups

Reporting group title	Intervention
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Reporting group description:

The intervention was composite in nature, comprising a varnish containing 22,600 parts per million (p.p.m.) fluoride, a toothbrush and a 50-ml tube of toothpaste containing 1450 p.p.m. fluoride; plus standardised, evidence-based prevention advice provided at 6-monthly intervals over 3 years.

Reporting group title	Control
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Reporting group description:

The control group received standardised caries prevention advice alone at 6-monthly intervals over 3 years.

Serious adverse events	Intervention	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 624 (7.21%)	37 / 624 (5.93%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	1 / 624 (0.16%)	1 / 624 (0.16%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	9 / 624 (1.44%)	5 / 624 (0.80%)	
occurrences causally related to treatment / all	0 / 9	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

General disorders and administration site conditions			
subjects affected / exposed	5 / 624 (0.80%)	7 / 624 (1.12%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	4 / 624 (0.64%)	5 / 624 (0.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory thoracic and mediastinal disorders			
subjects affected / exposed	10 / 624 (1.60%)	11 / 624 (1.76%)	
occurrences causally related to treatment / all	0 / 10	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 624 (0.16%)	1 / 624 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	1 / 624 (0.16%)	0 / 624 (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			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	7 / 624 (1.12%)	4 / 624 (0.64%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and infestations			

subjects affected / exposed	12 / 624 (1.92%)	9 / 624 (1.44%)	
occurrences causally related to treatment / all	0 / 13	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	1 / 624 (0.16%)	0 / 624 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	Intervention	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 624 (1.60%)	0 / 624 (0.00%)	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	5 / 624 (0.80%)	0 / 624 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	4 / 624 (0.64%)	0 / 624 (0.00%)	
occurrences (all)	4	0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 624 (0.16%)	0 / 624 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2010	Amendment 1 (substantial) was for the amendment of protocol version 12_12/05/2009 to protocol version 13_23/06/2010. This also included the delegation of signing authority for applications/submissions to MHRA and Ethics from Professor Martin Tickle as Chief Investigator to Dr Michael Donaldson the trial Principal Investigator.
23 March 2011	Amendment 2 (substantial) was submitted to ethics only. This was for the addition of a participant ID card.
22 December 2011	Amendment 3 (substantial) was for the amendment of protocol version 13_23/06/2010 to protocol version 14_19/08/2011.
16 June 2014	Amendment 5 (substantial) was submitted to ethics only. This was for the addition of a supplementary study to examine how being part of the trial impacted on oral health related parenting practices.
21 July 2014	Amendment 6 (substantial) was submitted to ethics only. This was for the addition of a letter to parents in advance of the 36 month visit.

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/27685609>

<http://www.ncbi.nlm.nih.gov/pubmed/28375708>

<http://www.ncbi.nlm.nih.gov/pubmed/28521109>