Clinical trial results:
A single blind study comparing the efficacy of Glycopyrronium and Hyoscine on drooling in children with neurodisability - DRI Trial (Drooling Reduction Intervention)

Summary

EudraCT number	2013-000863-94
Trial protocol	GB
Global end of trial date	31 January 2017

Results information

Result version number	v1 (current)
This version publication date	05 January 2019
First version publication date	05 January 2019

Trial information

Trial identification

Sponsor protocol code	6474

Additional study identifiers

ISRCTN number	ISRCTN75287237
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC : 13/NE/0078

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Regent Point, Regent Farm Road, Newcastle upon Tyne, United Kingdom, NE3 3HD
Public contact	Dr Parr, Chief Investigator, Newcastle University, 44 0191 282 5966, jeremy.parr@ncl.ac.uk
Scientific contact	Dr Parr, Chief Investigator, Newcastle University, 44 0191 282 5966, jeremy.parr@ncl.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	21 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2017
Global end of trial reached?	Yes
Global end of trial date	31 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To identify whether Glycopyrronium or Hyoscine is more effective in treating drooling in children with non-progressive disability

Protection of trial subjects:

The trial involved an independent Data Monitoring Committee (DMC) and Trial Steering Commitee to provide overall supervision for the trial on behalf of the Trial Sponsor and Trial Funder and to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the trial.

Background therapy:

Drooling is due to oromotor impairment, and is a common problem in children with neurodevelopmental disorders. The negative consequences of drooling for children and their relatives include skin breakdown to the child’s chin, dehydration, and damage to clothing and equipment such as electronic communication aids. Children, siblings and parents often suffer social embarrassment due to drooling. There is no evidence about the relative effectiveness of the two medications most commonly used to reduce drooling.

There are only limited data about their side effects and how acceptable they are to children and parents; this lack of information makes it difficult for children, parents and doctors to make informed decisions about which drug to use, and at what dose.

This study will determine whether there is a difference in the effectiveness of the medications, and which doses are associated with fewest side effects. This information will be used to develop evidence based guidance to help children, parents and doctors firstly to decide which medication to prescribe to reduce problematic drooling and at what dose; secondly to show how adverse effects can be monitored, and when dosage should be reduced or medication stopped.

The study will benefit children with neurodisability who drool and their families. By identifying how best to choose medication, decide on dosage and monitor effect and side effects, this applied research study relates to day to day practice of health service staff – specifically paediatricians and speech and language therapists. Children’s drooling will be better controlled with the accompanying physical and psychosocial benefits for child and family.

Evidence for comparator:

Medication is the first intervention used by most UK clinicians and helps many children; both Hyoscine and Glycopyrronium work by reducing cholinergic stimulation of salivary glands, and the volume of saliva produced.
There is a lack of research evidence about which of the two most commonly used medications works best, and which is best tolerated. Glycopyrronium is an oral medication (liquid) and hyoscine a skin patch; a double blind trial was therefore not appropriate.. The most effective dose and regime to increase doses is not known. The study involved escalating doses up to a maximum suggested in the British National Formulary for Children.

The medication regime:

1. Glycopyrronium study arm
Week 1: 40mcg/kg/ per dose
Week 2, 60mcg/kg/ per dose
Week 3, 80mcg/kg/ per dose

Week 4, 100mcg/kg/ per dose
All doses three times a day. Adjusted according to response up to maximum 2 mg per dose per day

2. Hyoscine study arm
Week one ¼ patch, week two ½ patch, week three ¾ patch, week four full patch
The patch will be replaced every three days, alternating sites to minimise the risk of a local skin reaction. The patch will not be cut (this results in loss of absorption), but an occlusive dressing will be used as per usual clinical practice.

Actual start date of recruitment	01 September 2013
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: 90
Worldwide total number of subjects	90
EEA total number of subjects	90

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)	85
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In the course of normal clinical practice, parents/guardians and the local paediatrician would determine if a child needed medication for drooling. If it was the case, the local paediatrician the trial approached the family regarding the child's potential participation in the study.

Pre-assignment

Screening details:

Recruitment was conducted by the local paediatrician during standard clinical care visit, so that only children who were deemed by the clinician and the family to need treatment for drooling were invited to participate. Parent/Guardian were provided with an Information Sheet and an opportunity to ask any questions about the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Randomised trial of two medication regimes known to patient and clinician but not the Trial Outcome Assessor.

Arms

Are arms mutually exclusive?	Yes
Arm title	Glycopyrronium

Arm description:

Children randomised to glycopyrronium liquid received three doses per day: week-1: 40 µg/kg/per dose; week-2: 60 µg/kg/per dose; week-3: 80 µg/kg/ per dose; week-4: 100 µg/kg/per dose to a maximum 2 mg per dose. Medication was given orally or by feeding tube.
Please note the number of participants started refers to the number of participants randomised to the trial. Five participants withdrew prior to receiving any treatment on the trial.

Arm type	Active comparator
Investigational medicinal product name	Glycopyrronium Bromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

The medication regime for participants randomised to the Glycopyrronium study arm:
Week 1: 40mcg/kg/ per dose
Week 2, 60mcg/kg/ per dose
Week 3, 80mcg/kg/ per dose
Week 4, 100mcg/kg/ per dose
All doses three times a day. Adjusted according to response up to maximum 2 mg per dose per day.

Trial medication continued for 12 weeks after which all trial medication was then returned. At the end of week 12, the Trial Research Paediatrician contacted the parent again to remind
them of a pre-arranged appointment with their usual local paediatrician. Their local paediatrician will discussed with the parents whether their child should continue on the same
medication (locally prescribed) or use alternative management.

Arm title	Hyoscine

Arm description:

Children randomised to the hyoscine received the following regime:
week-1: ¼ patch; week-2: ½ patch; week-3: ¾ patch; week-4: full patch. The patch was typically placed below an ear with an occlusive dressing applied over and replaced every 3 days, alternating sites to minimise local skin reaction risk. The plastic patch backing was cut to expose the prescribed portion

of the patch; the patch itself was not cut to avoid leakage of product from the non-loculated reservoir. Please note the number of participants started refers to the number of participants randomised to the trial. Five participants withdrew prior to receiving any treatment on the trial.

Arm type	Active comparator
Investigational medicinal product name	Hyoscine
Investigational medicinal product code	
Other name	Scopoderm
Pharmaceutical forms	Transdermal patch
Routes of administration	Transdermal use

Dosage and administration details:

Transdermal patch containing 1.5mg hyoscine.
Hyoscine patches 1mg/72 hours were provided as a 12 week supply of patches; the patch was replaced every three das, alternating sites to minimise the risk of a local skin reaction.

Treatment schedule:
Week one 1/4 patch, week two 1/2 patch, week three 3/4 patch, week four full patch.

Number of subjects in period 1	Glycopyrronium	Hyoscine
Started	41	49
4 week outcome	33	35
12 week outcome	31	26
Completed	31	26
Not completed	10	23
Not right time to participate in a trial	-	1
Adverse event, non-fatal	7	21
Family Illness	1	-
Concern about side effects	1	1
Drooling no longer a problem	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Glycopyrronium
Reporting group description:	
Children randomised to glycopyrronium liquid received three doses per day: week-1: 40 µg/kg/per dose; week-2: 60 µg/kg/per dose; week-3: 80 µg/kg/ per dose; week-4: 100 µg/kg/per dose to a maximum 2 mg per dose. Medication was given orally or by feeding tube. Please note the number of participants started refers to the number of participants randomised to the trial. Five participants withdrew prior to receiving any treatment on the trial.	
Reporting group title	Hyoscine
Reporting group description:	
Children randomised to the hyoscine received the following regime: week-1: ¼ patch; week-2: ½ patch; week-3: ¾ patch; week-4: full patch. The patch was typically placed below an ear with an occlusive dressing applied over and replaced every 3 days, alternating sites to minimise local skin reaction risk. The plastic patch backing was cut to expose the prescribed portion of the patch; the patch itself was not cut to avoid leakage of product from the non-loculated reservoir. Please note the number of participants started refers to the number of participants randomised to the trial. Five participants withdrew prior to receiving any treatment on the trial.	

Reporting group values	Glycopyrronium	Hyoscine	Total
Number of subjects	41	49	90
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Ninety children from 15 UK National Health Service (NHS) neurodevelopmental teams recruited over 17 months.			
Units: years			
median	4.6	4.9	
full range (min-max)	3.0 to 11.9	3.0 to 14.5	-
Gender categorical Units: Subjects			
Female	19	16	35
Male	22	33	55
Severity of drooling Units: Subjects			
Saliva usually on clothes	35	43	78
Saliva usually on face	6	6	12
Weight Units: Kg			
median	16.6	18.1	
full range (min-max)	10.4 to 41.8	11.1 to 79.4	-

End points

End points reporting groups

Reporting group title	Glycopyrronium

Reporting group description:

Children randomised to glycopyrronium liquid received three doses per day: week-1: 40 µg/kg/per dose; week-2: 60 µg/kg/per dose; week-3: 80 µg/kg/ per dose; week-4: 100 µg/kg/per dose to a maximum 2 mg per dose. Medication was given orally or by feeding tube.
Please note the number of participants started refers to the number of participants randomised to the trial. Five participants withdrew prior to receiving any treatment on the trial.

Reporting group title	Hyoscine

Reporting group description:

Children randomised to the hyoscine received the following regime:
week-1: ¼ patch; week-2: ½ patch; week-3: ¾ patch; week-4: full patch. The patch was typically placed below an ear with an occlusive dressing applied over and replaced every 3 days, alternating sites to minimise local skin reaction risk. The plastic patch backing was cut to expose the prescribed portion of the patch; the patch itself was not cut to avoid leakage of product from the non-loculated reservoir.
Please note the number of participants started refers to the number of participants randomised to the trial. Five participants withdrew prior to receiving any treatment on the trial.

Primary: Drooling Impact Scale (DIS) score at 4 weeks

End point title	Drooling Impact Scale (DIS) score at 4 weeks

End point description:

End point type	Primary

End point timeframe:

Drooling Impact Scale (DIS) score at 4 weeks

End point values	Glycopyrronium	Hyoscine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	41		
Units: number				
arithmetic mean (standard deviation)	25.3 (± 14.1)	32.1 (± 19.4)		

Statistical analyses

Statistical analysis title	Difference in mean scores week 4 DIS Scores
Comparison groups	Hyoscine v Glycopyrronium
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	6.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	15.3
Variability estimate	Standard error of the mean
Dispersion value	4.2

Primary: Sensitivity analysis of the primary outcome measure: Week 4 DIS Score

End point title	Sensitivity analysis of the primary outcome measure: Week 4 DIS Score

End point description:

The analysis set is the treatment tolerated set.
This analysis repeats the analysis of the primary outcome measure, however, rather than an ITT analysis, only those patients who tolerated their treatment and were still on the treatment to which randomised at week 4 are included.
Of the 70 patients included in the ITT analysis of the primary outcome, 58 were still on the treatment to which randomised at week 4.

End point type	Primary

End point timeframe:

Week 4 DIS Score

End point values	Glycopyrronium	Hyoscine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	33		
Units: number				
arithmetic mean (standard deviation)	21.9 (± 11.7)	26.2 (± 15.5)		

Statistical analyses

Statistical analysis title	Difference in mean scores week 4 DIS Scores
Comparison groups	Glycopyrronium v Hyoscine
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.2
upper limit	11.8
Variability estimate	Standard error of the mean
Dispersion value	3.7

Secondary: Week-12 DIS Scores

End point title	Week-12 DIS Scores
End point description:	
The analysis set is the Intention to treat (ITT) set.	
End point type	Secondary
End point timeframe:	
Week-12 DIS Scores	

End point values	Glycopyrronium	Hyoscine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	38		
Units: number				
arithmetic mean (standard deviation)	23.8 (± 17.5)	31.0 (± 19.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Drooling Severity-Frequency Scale (DSFS) score at baseline

End point title	Change in Drooling Severity-Frequency Scale (DSFS) score at baseline
End point description:	
The analysis set is the Treatment Tolerated Set.	
End point type	Secondary
End point timeframe:	
Baseline	

End point values	Glycopyrronium	Hyoscine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	35		
Units: number				
arithmetic mean (standard deviation)	7.6 (± 1.1)	7.6 (± 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Drooling Severity-Frequency Scale (DSFS) score at week 4

End point title	Change in Drooling Severity-Frequency Scale (DSFS) score at week 4

End point description:

The analysis set is the Treatment Tolerated Set.

End point type	Secondary

End point timeframe:

week 4

End point values	Glycopyrronium	Hyoscine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	35		
Units: number				
arithmetic mean (standard deviation)	4.7 (± 1.9)	5.1 (± 1.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Drooling Severity-Frequency Scale (DSFS) score at week 12

End point title	Change in Drooling Severity-Frequency Scale (DSFS) score at week 12

End point description:

The analysis set is the Treatment Tolerated Set.

End point type	Secondary

End point timeframe:

week 12

End point values	Glycopyrronium	Hyoscine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	25		
Units: number				
arithmetic mean (standard deviation)	4.7 (± 1.9)	4.7 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Treatment Satisfaction Questionnaire for Medication (TSQM) score at 4 weeks

End point title	Change in Treatment Satisfaction Questionnaire for Medication (TSQM) score at 4 weeks

End point description:

TSQM is a series of 11 questions coded and scored into 4 scales: effectiveness, side effects, convenience, global satisfaction. Each scale score is generated from selected questions and scaled to range from 0 to 100.
Effectiveness: 0 extremely dissatisfied, 100 extremely satisfied
Side effects: 0 extremely dissatisfied, 100 not at all dissatisfied
Convenience: 0 extremely dissatisfied, 100 extremely satisfied
Global satisfaction: 0 extremely dissatisfied, 100 extremely satisfied

End point type	Secondary

End point timeframe:

4 week

End point values	Glycopyrronium	Hyoscine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: number				
arithmetic mean (standard deviation)				
Effectiveness	86.8 (± 9.8)	79.5 (± 17.2)		
Side Effects	98.1 (± 5.1)	96.0 (± 13.4)		
Convenience	85.8 (± 12.0)	79.1 (± 15.2)		
Global score	86.3 (± 13.5)	74.5 (± 15.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Week 12 DIS score- treatment tolerated set (TT)

End point title	Week 12 DIS score- treatment tolerated set (TT)

End point description:

The analysis set is the treatment tolerated set.
Only those patients who tolerated their treatment and were still on the treatment to which randomised at week 12 are included in this analysis.
57 patients were still on the treatment to which randomised at week 12.
1 was still on treatment at week 12 but no DIS score was available.
4 had DIS assessments outside the required window (80 to 91 days inclusive).

End point type	Secondary

End point timeframe:

Week 12

End point values	Glycopyrronium	Hyoscine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	23		
Units: number				
arithmetic mean (standard deviation)	19.6 (± 12.1)	21.9 (± 11.4)		

Statistical analyses

Statistical analysis title	Difference in mean scores week 12 DIS Scores
Statistical analysis description: The analysis set is the treatment tolerated set.	
Comparison groups	Glycopyrronium v Hyoscine
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	9
Variability estimate	Standard error of the mean

Secondary: Comparison of week 4 vs week 12 DIS Scores

End point title	Comparison of week 4 vs week 12 DIS Scores
End point description: Paired t-test. Results shown for each group separately.	
End point type	Secondary
End point timeframe: Comparison of week 4 vs week 12 DIS Scores	

End point values	Glycopyrronium	Hyoscine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	36		
Units: number				
arithmetic mean (standard error)	-1.1 (± 3.0)	1.4 (± 4.3)		

Statistical analyses

Statistical analysis title	Comparison of week 4 vs week 12 Glycopyrronium
Comparison groups	Hyoscine v Glycopyrronium
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	5.2
Variability estimate	Standard error of the mean
Dispersion value	3

Statistical analysis title	Comparison of week 4 vs week 12 Hyoscine
Comparison groups	Hyoscine v Glycopyrronium
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	10
Variability estimate	Standard error of the mean
Dispersion value	4.3

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Adverse Events will be recorded from randomisation to 52 week follow up.	
Assessment type	Systematic

Dictionary used	
Dictionary name	verbatim
Dictionary version	1

Reporting groups	
Reporting group title	Hyoscine
Reporting group description: -	
Reporting group title	Glycopyrronium
Reporting group description: -	

Serious adverse events	Hyoscine	Glycopyrronium	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 47 (2.13%)	1 / 38 (2.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Gastroenteritis requiring IVs			
subjects affected / exposed	0 / 47 (0.00%)	1 / 38 (2.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture left leg			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (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: 0 %

Non-serious adverse events	Hyoscine	Glycopyrronium	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 47 (70.21%)	6 / 38 (15.79%)	
Surgical and medical procedures			

Planned surgery			
subjects affected / exposed	0 / 47 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Ataxia/Wobbliness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
disturbed sleep, sleepwalking			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Hallucinations and hyperactivity			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
new secondary nocturnal enuresis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
possible brief seizure			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Decreased urinary frequency			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Did not tolerate wearing patch/ plaster. Did not like it.			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
early morning waking and hyperactivity			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Oral bleed			
subjects affected / exposed	0 / 47 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	2	

macular papular rash on sternum			
subjects affected / exposed	0 / 47 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Floppiness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Hyper episode at night unable to sleep			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Hyperactivity			
subjects affected / exposed	1 / 47 (2.13%)	1 / 38 (2.63%)	
occurrences (all)	1	1	
hyperactivity and deterioration in behaviour			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
local reaction to hyoscine			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Local skin reaction			
subjects affected / exposed	8 / 47 (17.02%)	0 / 38 (0.00%)	
occurrences (all)	12	0	
local skin reaction, delayed sensitivity			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
local skin reaction to dressing			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Local skin reaction to hyoscine			
subjects affected / exposed	3 / 47 (6.38%)	0 / 38 (0.00%)	
occurrences (all)	4	0	
local skin reaction to patch			
subjects affected / exposed	2 / 47 (4.26%)	0 / 38 (0.00%)	
occurrences (all)	2	0	
local skin reaction, swelling and precipitated run of seizures within 30 minutes of applying patch			

subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Local skin reaction, red demarcated area under patch			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Local skin reaction, continued wks 11&12 & after trial. Continued patches 3 more months then stopped			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
overdrying of mouth			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
patches recurrently falling off			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Repeated pulling off of patch			
subjects affected / exposed	3 / 47 (6.38%)	0 / 38 (0.00%)	
occurrences (all)	3	0	
self injury behaviour			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
sleepiness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
standing and falling to floor, no loss of consciousness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
wobbliness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
allergic type reaction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Eye disorders			

visual blurring week 3			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 47 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
Diarrhoea and vomiting			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
cough, illness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
excessive drying of secretions	Additional description: excessive drying of secretions sufficient enough to warrant mother deciding to stop		
subjects affected / exposed	0 / 47 (0.00%)	1 / 38 (2.63%)	
occurrences (all)	0	1	
rash			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
redness and dry marks under patch			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
redness and itch under patch			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	
redness under the plaster			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
Fracture right arm			
subjects affected / exposed	1 / 47 (2.13%)	0 / 38 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 July 2013	Substantial amendment 1 involved: The removal of the SMPC for Hyoscine and Glycopyrronium from the protocol appendices. Revision of the fax number for notifying SAEs and pregnancy. Addition and removal of the sites who will take part in the trial. Change of PI at Newcastle upon Tyne Hospitals NHS Foundation Trust.
17 September 2013	Administrative changes to protocol and CTA. Participant Information Sheet modified to include instructions to parents regarding the application of the occlusive dressing. Updates to monitoring of the study. Revised sIMPD confirming Glycopyrronium shelf life (6 months). Introduction of diary cards to record dose adjustments. Introduction of a nurses letter.
12 March 2014	Addition of trial sites.
20 June 2014	Addition of a trial site.
31 July 2014	Addition of sites.
14 November 2014	Update to sIMPD. Update to protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported