Clinical trial results:
A single-Centre, open-label, exploratory study of the effect of 20 mg ambroxol hydrochloride on cough reflex sensitivity in patients with acute cough.

Summary

EudraCT number	2017-003980-36
Trial protocol	GB
Global end of trial date	19 April 2018

Results information

Result version number	v1 (current)
This version publication date	19 January 2020
First version publication date	19 January 2020
Summary attachment (see zip file)	final report (Revised Final Report IIT170718 version 1 _cew_.docx)

Trial information

Trial identification

Sponsor protocol code	IIT15419

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Hull University Teaching Hospitals NHS Trust
Sponsor organisation address	Anlaby road, Hull, United Kingdom, HU3 2JZ
Public contact	Caroline Wright, University of Hull, 01482 01482624067, c.e.wright@hull.ac.uk
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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	02 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 April 2018
Global end of trial reached?	Yes
Global end of trial date	19 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•To assess the effect of a single dose of 20 mg ambroxol lozenge on cough reflex sensitivity in patients with acute cough. Cough sensitivity will be measured using an artificially induced cough model, stimulating cough with four different types of challenge agents (citric acid,capsaicin,ATP and distilled water).

Protection of trial subjects:

none

Background therapy:

None

Evidence for comparator:

Not applicable

Actual start date of recruitment	12 December 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	12
From 65 to 84 years	2

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was an open label, single centre exploratory study in patients with acute cough related to respiratory tract infection.
Recruitment took place at Castle Hill Hospital only and patients were recruited through local poster. recruitment started in February 2018 and ended March 20!8.

Pre-assignment

Screening details:

Males/Females 18–80 years were screened, with acute cough and other symptoms consistent with a common cold or an acute upper respiratory tract infection (URTI) diagnosis. The subjects had onset of symptoms within 72 h of study enrolment; and a Cough Severity VAS ≥ 40 mm at Screening; All subjects coughed at least twice to all cough challenge agents

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

No blinding for this study, measurements of cough sensitivity was done at baseline and post 20 mg Ambroxol at 30 and 9o min post dose

Arms

Arm title	baseline
Arm description: -	
Arm type	no intervention
Investigational medicinal product name	Ambroxol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Baseline period NO INTERVENTION. Ambroxol administered following baseline measuresadministered by nurse to patient one single 20mg tablet to be sucked until dispersed

Number of subjects in period 1	baseline
Started	14
Completed	14

Period 2	
Period 2 title	30 min ambrox
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Arm title	30 min post Ambroxol treatment

Arm description:
post 20 mg ambroxol oral lozenge

Arm type	Experimental
Investigational medicinal product name	Ambroxol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:
administered by nurse to patient one single 20mg tablet to be sucked until dispersed

Number of subjects in period 2	30 min post Ambroxol treatment
Started	14
Completed	14

Period 3	
Period 3 title	90 min post ambrox
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms	
Arm title	90 min post treatment

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ambroxol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:
administered by nurse to patient one single 20mg tablet to be sucked until dispersed

Number of subjects in period 3	90 min post treatment
Started	14
Completed	14

Period 4	
Period 4 title	recovery
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	recovery
Arm description: -	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 4	recovery
Started	14
Completed	13
Not completed	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	14	14	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	2	2	
85 years and over	0	0	
Age continuous			
population-adults with acute cough			
Units: years			
arithmetic mean	45.9		
standard deviation	± 12.6	-	
Gender categorical Units: Subjects			
Female	13	13	
Male	1	1	

End points

End points reporting groups

Reporting group title	baseline
Reporting group description: -	
Reporting group title	30 min post Ambroxol treatment
Reporting group description: post 20 mg ambroxol oral lozenge	
Reporting group title	90 min post treatment
Reporting group description: -	
Reporting group title	recovery
Reporting group description: -	

Primary: cough reflex sensitivity ATP (C2)

End point title	cough reflex sensitivity ATP (C2)[1]
End point description: Concentration of ATP causing 2 or more coughs (C2)	
End point type	Primary
End point timeframe: Recorded at baseline, at 30 min post 20 mg ambroxol treatment, 90 minutes post Ambroxol and following recovery of URTI	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: study was a crossover thus no reporting of statistics as system unable to distinguish this

End point values	30 min post Ambroxol treatment	90 min post treatment	recovery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	14	13	
Units: micromole(s)				
arithmetic mean (standard deviation)	2.27 (± 2.32)	2.52 (± 1.52)	3.42 (± 2.67)	

Statistical analyses

No statistical analyses for this end point

Primary: cough reflex sensitivity distilled water (C2)

End point title	cough reflex sensitivity distilled water (C2)[2]
End point description: measuring % distilled water causing 2 or more coughs	
End point type	Primary
End point timeframe: cough sensiivity to distilled water where two or more coughs C2 measured at baseline, and 30 min,90 min post 20 mg ambroxol and at recovery	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: study was a crossover thus no reporting of statistics as system unable to distinguish this

End point values	30 min post Ambroxol treatment	90 min post treatment	recovery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	14	13	
Units: log percent				
arithmetic mean (standard deviation)	4.39 (± 0.49)	4.16 (± 0.45)	4.51 (± 0.34)	

Statistical analyses

No statistical analyses for this end point

Primary: cough reflex sensitivity citric acid (C2)

End point title	cough reflex sensitivity citric acid (C2)[3]

End point description:

measuring log concentration of citric acid causing 2 or more coughs

End point type	Primary

End point timeframe:

measuring cough sensitivity to citric acid during upper respiratory tract infection and at 30min, 90 min post 20 mg ambroxol and at recovery from URTI.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: study was a crossover thus no reporting of statistics as system unable to distinguish this

End point values	30 min post Ambroxol treatment	90 min post treatment	recovery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	14	13	
Units: log mM				
arithmetic mean (standard deviation)	4.83 (± 1.64)	4.83 (± 1.2)	4.93 (± 1.7)	

Statistical analyses

No statistical analyses for this end point

Primary: cough reflex sensitivity capsaicin (c2)

End point title	cough reflex sensitivity capsaicin (c2)[4]

End point description:

End point type	Primary

End point timeframe:

cough reflex sensitivity to capsaicin measured at baseline and at 30 min ,90 min ambroxol and at

recovery

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: study was a crossover thus no reporting of statistics as system unable to distinguish this

End point values	30 min post Ambroxol treatment	90 min post treatment	recovery	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	14	13	
Units: log Micro M				
arithmetic mean (standard deviation)	2.19 (± 1.79)	2.52 (± 1.52)	2.80 (± 1.39)	

Statistical analyses

No statistical analyses for this end point

Secondary: cough severity VAS

End point title	cough severity VAS

End point description:

End point type	Secondary

End point timeframe:

Cough severity Vas measured at baseline at 30min and 90min post 20mg ambroxol and recovery

End point values	30 min post Ambroxol treatment	90 min post treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: mm				
arithmetic mean (standard deviation)	32.9 (± 1.4)	30.2 (± 1.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: urge to cough VAS

End point title	urge to cough VAS

End point description:

End point type	Secondary

End point timeframe:

measured at baseline at 30 min and 90 min post 20 mg ambroxol.

End point values	30 min post Ambroxol treatment	90 min post treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: mm				
arithmetic mean (standard deviation)	28.1 (± 2.4)	30.4 (± 1.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
adverse events were reported from consent up until patient completed the study. reported at baseline post 20 mg ambroxol and at recovery	
Adverse event reporting additional description:	
Adverse events were reported from signing of consent until patient completed study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	baseline
Reporting group description:	
All patients reports of Adverse events prior to any study related treatment	
Reporting group title	post 20 mg ambroxol
Reporting group description:	
all patients Adverse events reported following administration of 20 mg Ambroxol reported on the day of takin the study treatment.	
Reporting group title	recovery
Reporting group description:	
All patient returning for recovery visit, recording all adverse events since last sen in the unit.	

Serious adverse events	baseline	post 20 mg ambroxol	recovery
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	0 / 14 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	baseline	post 20 mg ambroxol	recovery
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 14 (14.29%)	3 / 14 (21.43%)	3 / 14 (21.43%)
Injury, poisoning and procedural complications			
Regurgitation	Additional description: regurgitation in response to cough challenge procedure		
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Nervous system disorders			

headache			
subjects affected / exposed	1 / 14 (7.14%)	1 / 14 (7.14%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatomegaly	Additional description: enlarged liver found prior to any therapy or procedures		
subjects affected / exposed	1 / 14 (7.14%)	0 / 14 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	1	1
Metabolism and nutrition disorders			
Muscle pain			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1

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? No

Limitations and caveats

None reported