Clinical trial results:
Effect of codeine on pharyngeal and esophageal motility in healthy subjects: a double-blind, placebo-controlled, randomized, cross-over study

Summary

EudraCT number	2017-002349-30
Trial protocol	BE
Global end of trial date	30 July 2019

Results information

Result version number	v1 (current)
This version publication date	04 February 2021
First version publication date	04 February 2021
Summary attachment (see zip file)	Article codeine study (nmo.14041.pdf)

Trial information

Trial identification

Sponsor protocol code	cod2017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03784105
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	TARGID
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Prof Jan Tack, TARGID, KU Leuven, 32 16344775 , jan.tack@kuleuven.be
Scientific contact	Prof Jan Tack, TARGID, KU Leuven, 32 16344775 , jan.tack@kuleuven.be

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 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 July 2019
Global end of trial reached?	Yes
Global end of trial date	30 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of codeine on pharyngeal and esophageal motility in healthy subjects

Protection of trial subjects:

Local anesthesia was provided in the nose to minimalize pain and discomfort during the placement of the nasogastric measuring probe.

Background therapy:

/

Evidence for comparator: -

Actual start date of recruitment	08 March 2018
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	Belgium: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	20
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Healthy volunteers will be selected via a database that is available in the lab and via mouth to mouth recruitment.

Pre-assignment

Screening details:

Inclusion: 18-60 year old, written informed consent before any study procedure, go home without driving a vehicle, will not operate machines on the study day, not pregnant or breastfeeding.
Exclusion: other significant diseases, upper GI symptoms or surgery, known side-effects to morphine/codeine, medication use (oral contraceptives allowed)

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	Subject

Blinding implementation details:

Codeine was inserted via a naso-gastric tube into the stomach to avoid recognition of the taste of codeine.

Arms

Are arms mutually exclusive?	No
Arm title	Codeine

Arm description:

We will administer the codeine intra-gastrically as a syrup: Bronchodine® 10mg/5ml.

Arm type	Experimental
Investigational medicinal product name	Bronchodine® 10mg/5ml
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Intragastric use

Dosage and administration details:

30 mL of Bronchodine® 10mg/5ml

Arm title	Placebo

Arm description:

As placebo we will administer the same volume (30 ml) of a glucose syrup, also intra-gastrically.

Arm type	Placebo
Investigational medicinal product name	Sirupus Simplex
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Intragastric use

Dosage and administration details:

As placebo we will administer the same volume (30 ml) of a glucose syrup (Siripus Simplex), also intra-gastrically.

Number of subjects in period 1	Codeine	Placebo
Started	20	19
Completed	19	19
Not completed	1	0
Adverse event, non-fatal	1	-

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	20	20	
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)	20	20	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	23.5		
standard deviation	± 0.6	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	5	5	

End points

End points reporting groups

Reporting group title	Codeine
Reporting group description:	
We will administer the codeine intra-gastrically as a syrup: Bronchodine® 10mg/5ml.	
Reporting group title	Placebo
Reporting group description:	
As placebo we will administer the same volume (30 ml) of a glucose syrup, also intra-gastrically.	

Primary: Integrated relaxation pressure 4s

End point title	Integrated relaxation pressure 4s
End point description:	
End point type	Primary
End point timeframe:	
comparison between two conditions	

End point values	Codeine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	19		
Units: mmHg				
median (inter-quartile range (Q1-Q3))	18 (15 to 21)	10 (8 to 14)		

Statistical analyses

Statistical analysis title	Mixed models primary endpoint
Statistical analysis description:	
Mixed models were constructed with the integrated relaxation pressure 4s as the dependent variable and and treatment condition (codeine or placebo) as within-subject independent, categorical variables.	
Comparison groups	Codeine v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	ANOVA

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events were reported for each patient from the start of visit 1 untill the end of visit 2.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	Codeine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The occurence of non-serious adverse events was below 5%

Serious adverse events	Codeine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
biliary type pain			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Codeine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	

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