



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 minimize 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 until 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 occurrence 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