



Clinical trial results:

Dose-dependent effects of propranolol on extinction learning and return of fear

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2018-003409-25 |
| Trial protocol | BE |
| Global end of trial date | 16 June 2021 |

Results information

| | |
|--------------------------------|---|
| Result version number | v2 (current) |
| This version publication date | 22 September 2022 |
| First version publication date | 19 March 2022 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data set In the previous version, US expectancy data had not been treated for missing values (unlike our other outcome measures). We treated the data, repeated the analysis, and provide the new results here. It should be noted that the pattern of results did not change. |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | S61887 |
|-----------------------|--------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | KU Leuven |
| Sponsor organisation address | Tiensestraat 102 bus 3712, Leuven, Belgium, 3000 |
| Public contact | Prof. Dr. Tom Beckers, KU Leuven, +32 016326134, tom.beckers@kuleuven.be |
| Scientific contact | Prof. Dr. Tom Beckers, KU Leuven, +32 016326134, tom.beckers@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 | 11 October 2021 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 June 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

In our previous study (2016-002392-10; S59302), we found evidence that 40 mg oral administration of Propranolol HCl 60 min prior to extinction training attenuates fear responding and facilitates extinction. Propranolol administration did not prevent the return of fear, however, we did not test for return of fear in absence of the drug. The main aim of the present study is to investigate whether propranolol has a dose-dependent effect on extinction learning, and whether this further prevents the return of fear, in absence of the drug.

Protection of trial subjects:

During all testing days, the experimenter remained in an adjacent room and had one-way visual contact with the subjects at all times. Subjects were informed that they could stop the experiment at any point, without giving reason and without being penalized. At the end of the experiment, we provided the subjects with the contact details of several support services in case they needed further assistance after completion of the experiment or had the urge to talk to somebody (other than the researchers) about it. These people were prepared to talk to the subjects immediately or get back to them (e.g., contact by e-mail). Contact information included clinical psychologists from within, as well as from outside our department, the student health services, and a call center where you can speak to someone anonymously.

Background therapy:

None.

Evidence for comparator:

We used a placebo, a commonly used comparator. Placebos were used as they did not contain any active substance that could exert effects upon consumption. Placebo pills were manufactured to be perceptually matched to the active drug (Propranolol). All medication was packaged in the same neutral package that was only labeled with a subject number. Labelling was done by the university hospital pharmacy. These steps were taken as to maintain a double-blind experimental procedure, thus preventing any undue influence on the results from expectations/demands of the subjects or the researcher.

| | |
|---|---------------|
| Actual start date of recruitment | 04 March 2019 |
| 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: 152 |
| Worldwide total number of subjects | 152 |
| EEA total number of subjects | 152 |

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) | 152 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Healthy, adult subjects were recruited from 04/03/2019 until 16/06/2021 through a database of potential research participants, managed by the KU Leuven Faculty of Psychology and Educational Sciences (Experiment Management System, EMS, accessible at psykuleuven.sona-systems.com).

Pre-assignment

Screening details:

Subjects were screened on Days 1 and 2, before being assigned to the arms of the study. Day 1 screening: 1) Medical exclusion criteria, 2) The Anxiety Sensitivity Index questionnaire (ASI), and 3) Non-differentiation between CS+ and CS-, on the last block of acquisition, in FPS. Day 2 screening: Medical exclusion criteria. See pre-assignment period

Pre-assignment period milestones

| | |
|------------------------------|-----|
| Number of subjects started | 152 |
| Number of subjects completed | 73 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|--|
| Reason: Number of subjects | Medical exclusion criteria (Day 2): 3 |
| Reason: Number of subjects | Participant cancelled appointment: 3 |
| Reason: Number of subjects | Screening questionnaire cutoff (ASI): 11 |
| Reason: Number of subjects | Medical exclusion criteria (Day 1): 20 |
| Reason: Number of subjects | Non-differentiation CS+/CS- (end of Day 1): 42 |

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Overall period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

An external collaborator not involved in the study randomized subjects into three groups matched on age, gender, trait anxiety (STAI-T), and anxiety sensitivity (ASI).

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 80 mg Propranolol |

Arm description:

In this arm, subjects were administered 80 mg Propranolol on Day 2 of the experiment, 60 minutes prior to extinction learning.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Propranolol EG - 80 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were orally administered 2 tablets of 40 mg Propranolol EG simultaneously, for a combined dose of 80 mg.

| | |
|--|------------------------|
| Arm title | 40 mg Propranolol |
| Arm description: | |
| In this arm, subjects were administered 40 mg Propranolol on Day 2 of the experiment, 60 minutes prior to extinction learning. | |
| Arm type | Experimental |
| Investigational medicinal product name | Propranolol EG - 40 mg |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Subjects were orally administered 1 tablet of 40 mg Propranolol EG and 1 placebo tablet simultaneously. | |
| Arm title | Placebo |
| Arm description: | |
| In this arm, subjects were administered placebo on Day 2 of the experiment, 60 minutes prior to extinction learning. | |
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Subjects were orally administered 2 placebo tablets, simultaneously. | |

| Number of subjects in period 1^[1] | 80 mg Propranolol | 40 mg Propranolol | Placebo |
|---|-------------------|-------------------|---------|
| Started | 25 | 24 | 24 |
| Completed | 24 | 24 | 24 |
| Not completed | 1 | 0 | 0 |
| Excluded for not following instructions | 1 | - | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 152 subjects were originally recruited. 79 subjects were excluded during the pre-assignment period (see Subject disposition). 73 subjects were thus included in the baseline period.

Baseline characteristics

Reporting groups

| | |
|--|-------------------|
| Reporting group title | 80 mg Propranolol |
| Reporting group description: | |
| In this arm, subjects were administered 80 mg Propranolol on Day 2 of the experiment, 60 minutes prior to extinction learning. | |
| Reporting group title | 40 mg Propranolol |
| Reporting group description: | |
| In this arm, subjects were administered 40 mg Propranolol on Day 2 of the experiment, 60 minutes prior to extinction learning. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| In this arm, subjects were administered placebo on Day 2 of the experiment, 60 minutes prior to extinction learning. | |

| Reporting group values | 80 mg Propranolol | 40 mg Propranolol | Placebo |
|--|-------------------|-------------------|---------|
| Number of subjects | 25 | 24 | 24 |
| 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) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 25 | 24 | 24 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 21 | 19 | 20 |
| Male | 4 | 5 | 4 |

| Reporting group values | Total | | |
|--|-------|--|--|
| Number of subjects | 73 | | |
| 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) | 73 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |

| | | | |
|--------------------|----|--|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 60 | | |
| Male | 13 | | |

End points

End points reporting groups

| | |
|--|-------------------|
| Reporting group title | 80 mg Propranolol |
| Reporting group description: In this arm, subjects were administered 80 mg Propranolol on Day 2 of the experiment, 60 minutes prior to extinction learning. | |
| Reporting group title | 40 mg Propranolol |
| Reporting group description: In this arm, subjects were administered 40 mg Propranolol on Day 2 of the experiment, 60 minutes prior to extinction learning. | |
| Reporting group title | Placebo |
| Reporting group description: In this arm, subjects were administered placebo on Day 2 of the experiment, 60 minutes prior to extinction learning. | |

Primary: Fear-potentiated startle responding

| | |
|--|--|
| End point title | Fear-potentiated startle responding ^[1] |
| End point description: Values reported have been standardized, as is commonly done in this measure. To standardize the data, means and standard deviations from the first day were used to calculate within-participant z-scores. It is the z-scores that are reported below. | |
| End point type | Primary |
| End point timeframe: Fear-potentiated startle responding was measured throughout the experiment, but to assess the end point, we used the first trial during the retention testing phase on day 3 of the experiment. | |
| 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: See attached chart/documents for the statistical analysis. | |

| End point values | 80 mg Propranolol | 40 mg Propranolol | Placebo | |
|--------------------------------------|-------------------|-------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 24 | 24 | |
| Units: microvolts | | | | |
| arithmetic mean (standard deviation) | | | | |
| CS+ | 0.342 (± 1.136) | 0.593 (± 1.072) | 0.522 (± 0.989) | |
| CS- | -0.113 (± 0.915) | 0.356 (± 1.142) | 0.645 (± 1.106) | |
| NA | -1.006 (± 0.807) | -0.728 (± 1.141) | -0.873 (± 0.895) | |

| | |
|----------------------------|--|
| Attachments (see zip file) | FPS - Memory retention analysis/FPS - Memory retention |
|----------------------------|--|

Statistical analyses

No statistical analyses for this end point

Primary: Skin conductance response

| | |
|-----------------|--|
| End point title | Skin conductance response ^[2] |
|-----------------|--|

End point description:

Values reported have been standardized, as is commonly done in this measure. To standardize the data, means and standard deviations from the first day were used to calculate within-participant z-scores. It is the z-scores that are reported below.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Skin conductance responding was measured throughout the experiment, but to assess the end point, we used the first trial during the retention testing phase on day 3 of the experiment.

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: See attached chart/documents for the statistical analysis.

| End point values | 80 mg Propranolol | 40 mg Propranolol | Placebo | |
|--------------------------------------|----------------------|----------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 24 | 24 | |
| Units: microsiemens | | | | |
| arithmetic mean (standard deviation) | | | | |
| CS+ | 0.353 (± 1.524) | 0.548 (± 1.551) | 0.636 (± 1.494) | |
| CS- | 0.155 (± 1.577) | 0.015 (± 1.321) | 0.252 (± 1.499) | |

| | |
|----------------------------|--|
| Attachments (see zip file) | SCR - Memory retention analysis/SCR - Memory retention |
|----------------------------|--|

Statistical analyses

No statistical analyses for this end point

Primary: US expectancies

| | |
|-----------------|--------------------------------|
| End point title | US expectancies ^[3] |
|-----------------|--------------------------------|

End point description:

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Expectancies to receiving the US (i.e., shock to the wrist) were measured throughout the experiment, but to assess the end point, we used the first trial during the retention testing phase on day 3 of the experiment.

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: See attached chart/documents for the statistical analysis.

| End point values | 80 mg Propranolol | 40 mg Propranolol | Placebo | |
|---|----------------------|----------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 24 | 24 | 24 | |
| Units: Arbitrary units on a scale (-5 to 5) | | | | |
| arithmetic mean (standard deviation) | | | | |
| CS+ | -0.167 (± 3.226) | -0.250 (± 2.878) | 0.583 (± 2.749) | |
| CS- | -2.708 (± 2.422) | -2.667 (± 2.316) | -2.750 (± 2.625) | |

| | |
|-----------------------------------|---|
| Attachments (see zip file) | US expectancies - Memory retention analysis.pdf |
|-----------------------------------|---|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The researcher had to report all serious adverse events immediately to the sponsor except for those that the protocol identifies as not requiring immediate reporting.

Adverse event reporting additional description:

At the end of each testing day, subjects had to fill out an adverse events form which asked about possible adverse reactions during/following the experiment in general (e.g., dizziness, pain, strong negative feelings, etc.).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20 |

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | 40 mg Propranolol |
|-----------------------|-------------------|

Reporting group description:

In this arm, subjects were administered 40 mg Propranolol on Day 2 of the experiment, 60 minutes prior to extinction learning.

| | |
|-----------------------|-------------------|
| Reporting group title | 80 mg Propranolol |
|-----------------------|-------------------|

Reporting group description:

In this arm, subjects were administered 80 mg Propranolol on Day 2 of the experiment, 60 minutes prior to extinction learning.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

In this arm, subjects were administered placebo on Day 2 of the experiment, 60 minutes prior to extinction learning.

| Serious adverse events | 40 mg Propranolol | 80 mg Propranolol | Placebo |
|---|-------------------|-------------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 0 / 25 (0.00%) | 0 / 24 (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 | 40 mg Propranolol | 80 mg Propranolol | Placebo |
|---|-------------------|-------------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | 3 / 25 (12.00%) | 3 / 24 (12.50%) |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | 1 / 25 (4.00%) | 1 / 24 (4.17%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|--|--|---------------------|---------------------|
| Headache subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Pain | Additional description: At the wrist; the unconditioned stimulus (US; 200-ms shock) was administered there. | | |
| subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 1 / 25 (4.00%) 1 | 0 / 24 (0.00%) 0 |
| Ear and labyrinth disorders | | | |
| Difficulty hearing | Additional description: Noise blasts (90dB) were presented through headphones during the experiment to elicit fear-potentiated startle responding. | | |
| subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 |
| Gastrointestinal disorders | | | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 25 (0.00%) 0 | 1 / 24 (4.17%) 1 |
| Psychiatric disorders | | | |
| Strong negative feelings subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | 0 / 25 (0.00%) 0 | 0 / 24 (0.00%) 0 |

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? Yes

| Date | Interruption | Restart date |
|---------------|---|------------------|
| 12 March 2020 | Covid-19 pandemic; labs were shut down and all research paused. | 09 November 2020 |

Notes:

Limitations and caveats

None reported