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	v1
This version publication date	19 March 2022
First version publication date	19 March 2022

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	Screening questionnaire cutoff (ASI): 2
Reason: Number of subjects	Medical exclusion criteria (Day 1): 32
Reason: Number of subjects	Non-differentiation CS+/CS- (end of Day 1): 39
Reason: Number of subjects	Medical exclusion criteria (Day 2): 3
Reason: Number of subjects	Participant cancelled appointment: 3

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+	-0.190 (± 3.400)	-0.471 (± 3.223)	0.333 (± 2.763)	
CS-	-2.905 (± 2.528)	-2.647 (± 2.572)	-2.619 (± 2.692)	

Attachments (see zip file)	US expectancies - Memory retention analysis/US expectancies -

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	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.

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

Headache			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	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	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 24 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	0 / 24 (0.00%)
occurrences (all)	1	0	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	0 / 25 (0.00%)	0 / 24 (0.00%)	1 / 24 (4.17%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	1 / 24 (4.17%)
occurrences (all)	0	1	1
Psychiatric disorders			
Strong negative feelings			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	0 / 24 (0.00%)
occurrences (all)	0	1	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