Clinical trial results:
Reconsolidation interference versus retrieval interference as the basis for experimental amnesia in humans – The effect of drug state at memory retrieval

Summary

EudraCT number	2016-002392-10
Trial protocol	BE
Global end of trial date	23 June 2018

Results information

Result version number	v1 (current)
This version publication date	30 November 2020
First version publication date	30 November 2020
Summary attachment (see zip file)	Academic publication (Chalkia et al. (2019) Frontiers.pdf)

Trial information

Trial identification

Sponsor protocol code	S59302

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 - box 3712, Leuven, Belgium,
Public contact	PI Tom Beckers, KU Leuven, tom.beckers@kuleuven.be
Scientific contact	PI Tom Beckers, KU Leuven, 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	23 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 June 2018
Global end of trial reached?	Yes
Global end of trial date	23 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The effect of drug state on memory retrieval after induced experimental amnesia using Propranolol EG 40 mg. Our objective was to test whether the internal drug state induced by a single dose of propranolol (40 mg) was salient/potent enough to make later retrieval of a conditioned fear memory state-dependent.

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. 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). The counselor in case was Dr. Katleen Bogaerts (therapist and clinical psychologist). Prof. Dr. Lukas Van Oudenhove (MD) could be contacted regarding medical concerns, and for more general issues Marleen Gheldof (student counselor for KU Leuven students) was available.

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	23 March 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	Belgium: 85
Worldwide total number of subjects	85
EEA total number of subjects	85

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

Subject disposition

Recruitment

Recruitment details:

Healthy, adult subjects were recruited from 23/03/2017 until 21/06/2018 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:

On the first day of the experiment subjects were screened for numerous medical exclusion criteria (exclusion of 1 participant). At the end of the first day, 13 more subjects were excluded based on non-differentiation between CS+ and CS- on EMG. See pre-assignment period.

Pre-assignment period milestones

Number of subjects started	85
Number of subjects completed	71

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Met medical exclusion criterion: 1
Reason: Number of subjects	Exclusion criterion - non-differentiation CS+/CS-: 13

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 testing randomised subjects into four groups matched on age, gender, trait anxiety (STAI-T), anxiety sensitivity (ASI) and fear of spiders (FSQ).

Arms

Are arms mutually exclusive?	Yes
Arm title	Propranolol-Propranolol

Arm description:

In this arm, subjects were administered propranolol on the second day of the experiment, following memory reactivation. They were also administered propranolol on the third day of the experiment, prior to testing.

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 received one oral dose (40 mg) on the second day of the study and one oral dose (40 mg) on the third day of the study.

Arm title	Propranolol-Placebo

Arm description:

In this arm, subjects were administered propranolol on the second day of the experiment, following memory reactivation. They were administered placebo on the third day of the experiment, prior to testing.

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 received one oral dose (40 mg) on the second day of the study and one placebo tablet on the third day of the study (orally).

Arm title	Placebo-Placebo

Arm description:

In this arm, subjects were administered placebo on the second day of the experiment, following memory reactivation. They were also administered placebo on the third day of the experiment, prior to testing.

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 received one placebo tablet on the second day of the study and one placebo tablet on the third day of the study, orally.

Arm title	No Reactivation _Propranolol-Placebo

Arm description:

In this arm, subjects were administered propranolol on the second day of the experiment, without prior memory reactivation. They were administered placebo on the third day of the experiment, prior to testing.

Arm type	Active comparator
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 received one oral dose (40 mg) on the second day of the study and one placebo tablet on the third day of the study (orally).

Number of subjects in period 1[1]	Propranolol-Propranolol	Propranolol-Placebo	Placebo-Placebo
Started	19	16	19
Completed	15	15	15
Not completed	4	1	4
Subject had low BP and HR - exclusion criterion	1	-	-
Did not show up on the second/third day	1	1	2
Subject had a low HR - exclusion criterion	-	-	1
Pharmacy closed - could not receive medication	2	-	1

Number of subjects in period 1[1]	No Reactivation _Propranolol-Placebo
Started	17
Completed	15
Not completed	2
Subject had low BP and HR - exclusion criterion	-
Did not show up on the second/third day	1
Subject had a low HR - exclusion criterion	-
Pharmacy closed - could not receive medication	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: The worldwide number enrolled in the trial includes all subjects that were tested for at least one day, thus including those that were excluded at the end of the first day (see pre-assignment period) and were not randomised into one of the arms of the study (see baseline period).

Baseline characteristics

Reporting groups	
Reporting group title	Overall period

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	71	71	
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)	71	71	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	55	55	
Male	16	16	

End points

End points reporting groups

Reporting group title	Propranolol-Propranolol

Reporting group description:

In this arm, subjects were administered propranolol on the second day of the experiment, following memory reactivation. They were also administered propranolol on the third day of the experiment, prior to testing.

Reporting group title	Propranolol-Placebo

Reporting group description:

In this arm, subjects were administered propranolol on the second day of the experiment, following memory reactivation. They were administered placebo on the third day of the experiment, prior to testing.

Reporting group title	Placebo-Placebo

Reporting group description:

In this arm, subjects were administered placebo on the second day of the experiment, following memory reactivation. They were also administered placebo on the third day of the experiment, prior to testing.

Reporting group title	No Reactivation _Propranolol-Placebo

Reporting group description:

In this arm, subjects were administered propranolol on the second day of the experiment, without prior memory reactivation. They were administered placebo on the third day of the experiment, prior to testing.

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 average of the first 2 trials 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 results.

End point values	Propranolol-Propranolol	Propranolol-Placebo	Placebo-Placebo	No Reactivation _Propranolol-Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	15	15
Units: microvolts				
arithmetic mean (standard deviation)				
CS+	0.480 (± 0.598)	0.746 (± 0.597)	1.063 (± 0.579)	1.035 (± 0.856)
CS-	0.290 (± 0.850)	0.441 (± 0.637)	0.579 (± 0.527)	0.801 (± 0.836)
NA	-0.866 (± 0.695)	-0.275 (± 0.570)	-0.746 (± 0.373)	-0.075 (± 0.794)

Attachments (see zip file)	FPS_eudraCT.pdf

Statistical analyses

No statistical analyses for this end point

Primary: US expectancies

End point title	US expectancies[2]

End point description:

End point type	Primary

End point timeframe:

US expectancies 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:

[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 results.

End point values	Propranolol-Propranolol	Propranolol-Placebo	Placebo-Placebo	No Reactivation_Propranolol-Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15	15	15	15
Units: Arbitrary units on a scale (-5 to 5)				
arithmetic mean (standard error)				
CS+	3.733 (± 2.764)	3.200 (± 1.971)	3.800 (± 1.320)	3.933 (± 2.374)
CS-	-3.533 (± 2.386)	-3.692 (± 1.974)	-2.733 (± 2.404)	-2.467 (± 3.270)

Attachments (see zip file)	USexp_eudraCT.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Skin conductance responding

End point title	Skin conductance responding

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	Secondary

End point timeframe:

Skin conductance responding was measured throughout the experiment, but to assess the end point, we used the average of the first 2 trials during the retention testing phase on day 3 of the experiment.

End point values	Propranolol-Propranolol	Propranolol-Placebo	Placebo-Placebo	No Reactivation_Propranolol-Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	13	13	14
Units: microsiemens				
arithmetic mean (standard deviation)				
CS+	0.321 (± 0.959)	-0.181 (± 0.697)	0.454 (± 0.780)	-0.149 (± 0.650)
CS-	-0.172 (± 0.635)	-0.169 (± 0.690)	0.045 (± 0.833)	-0.385 (± 0.679)

Attachments (see zip file)	SCR_eudraCT.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

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.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Propranolol-Propranolol
Reporting group description: -	
Reporting group title	Propranolol-Placebo
Reporting group description: -	
Reporting group title	Placebo-Placebo
Reporting group description: -	
Reporting group title	No Reactivation_Propranolol-Placebo
Reporting group description: -	

Serious adverse events	Propranolol-Propranolol	Propranolol-Placebo	Placebo-Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	0 / 17 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	No Reactivation_Propranolol-Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Propranolol-Propranolol	Propranolol-Placebo	Placebo-Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 15 (0.00%)	0 / 17 (0.00%)

Non-serious adverse events	No		

	Reactivation_Propranolol-Placebo		
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 15 (0.00%)		

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: There were no non-serious adverse events. Propranolol is a licensed IMP and participants were medically screened before it was administered.

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30846933