Clinical trial results:
The noradrenergic basis of Parkinson’s tremor: a systems-level fMRI approach

Summary

EudraCT number	2016-004629-18
Trial protocol	NL
Global end of trial date	06 September 2021

Results information

Result version number	v1 (current)
This version publication date	16 September 2023
First version publication date	16 September 2023
Summary attachment (see zip file)	Main results summary (Main results summary.docx)

Trial information

Trial identification

Sponsor protocol code	helmich-veni-2016

Additional study identifiers

ISRCTN number	ISRCTN89589002
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Donders Institute
Sponsor organisation address	Kapittelweg 29, Nijmegen, Netherlands, PO Box 9101, 6500 HB
Public contact	Administration, Radboud University, Donders Institute for Brain, Cognition and Behaviour, 0031 243610750,
Scientific contact	Administration, Radboud University, Donders Institute for Brain, Cognition and Behaviour, 0031 243610750,

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	03 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2021
Global end of trial reached?	Yes
Global end of trial date	06 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the role of the noradrenergic system in the pathophysiology of PD tremor, by testing how a behavioral induction of noradrenergic activity (cognitive coactivation task) and a pharmacological inhibition of noradrenergic activity (propranolol versus placebo) both influenced tremor power (accelerometry) and tremor-related brain activity (fMRI) in tremor-dominant PD patients.

Protection of trial subjects:

First, we used extensive exclusion criteria and followed an extensive screening procedure including an interview over the telephone, a letter of the treating neurologist, and a repetition of all screening questions on both testing days. We performed an ECG either prior to propranolol intake, to rule out cardiac arrhythmias and bradycardia. In addition, we repeatedly measured heart rate before and after propranolol intake and performed constant monitoring of the subjects' heart rate and pupil during MRI scanning. Two researchers will be present at all times that will keep a close eye on the well-being of the participant, and to comfort the participant. If preferred, a partner could be present during all measurements performed.

Background therapy:

N.A.

Evidence for comparator:

N.A.

Actual start date of recruitment	01 September 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	Netherlands: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	35
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited through two sources: 1) Neurologists at the Radboudumc preselected patients during consultation or multidisciplinary meetings and 2) the online patient platform ParkinsonNEXT was used, where patients registered via the project webpage, or were sent an open invitation to participate if they fulfilled inclusion criteria.

Pre-assignment

Screening details:

Participants underwent an extensive phone screening prior to inclusion. Afterwards, medication use and PD diagnosis were checked check eligibility. At the start of the first visit, an ECG was recorded and checked by a medical doctor for any irregularities in rhythm and conductance that could indicate contraindications for propranolol.

Pre-assignment period milestones

Number of subjects started	64
Number of subjects completed	57

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 7

Period 1

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

Blinding implementation details:

Patients and assessing researchers did not know on which of the two testing days participants received propranolol and on which placebo. Dispersion of the propranolol tablet in water allows affordable blinding of the study subjects from treatment, as the inactive cellulose dispersed in water is indistinguishable from the dispersed tablet. Study medication was prepared by two qualified independent researchers before application. Deblinding happened after completion of all data collection.

Arms

Are arms mutually exclusive?	Yes
Arm title	Tremor-dominant group

Arm description:

27 participants passed all screening and pre-assignment. This means that these 27 patients received propranolol and placebo, in a cross-over design, in a counterbalanced order (double blind). 24 participants completed all test procedures.

Arm type	Experimental
Investigational medicinal product name	Propranolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Soluble tablet
Routes of administration	Oral use

Dosage and administration details:

single dose of 40 mg, administered orally, dissolved in water.

Investigational medicinal product name	Cellulose
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

One teaspoon of cellulose is dispersed in water by two independent researchers

Arm title	Non-tremor control group

Arm description:

This participant group was included to compare MRI measures, but did not receive any study medication.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Tremor-dominant group	Non-tremor control group
Started	27	30
Completed	24	29
Not completed	3	1
Adverse event, non-fatal	3	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: All tremor-dominant participants have an ECG and blood pressure assessment at the start of the first testing day. At that time, they have been included in the trial, but if they do not meet all inclusion criteria they will not be allocated to the intervention (propranolol). For 7 patients, the ECG or blood pressure assessments showed irregularities and these patients thus were not allocated to receive study medication.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description:

This number is incorrect, but I cannot change it. It is 64: 30 in the non-tremor group and 34 in the tremor-dominant group.

Reporting group values	Overall trial	Total	
Number of subjects	57	57	
Age categorical Units: Subjects			
Adults (18-64 years)	32	32	
From 65-84 years	25	25	
Age continuous Units: years			
arithmetic mean	56		
full range (min-max)	46 to 76	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	42	42	
Disease duration Units: years			
arithmetic mean	4.8		
standard deviation	± 3.4	-	

Subject analysis sets	
Subject analysis set title	Clinical effects of propranolol on different PD tremor types
Subject analysis set type	Per protocol

Subject analysis set description:

To explore the effect of cognitive load as well as propranolol on resting tremor outside of the MRI context, we performed a two-way repeated measures-analysis of variance (ANOVA) with the log-transformed tremor amplitude (averaged across two repetitions per condition) as dependent variable, and the two within-subject variables TRIAL (rest vs. coco trials) and DRUG (propranolol vs. placebo session). For the remaining two tremor conditions (postural tremor and kinetic tremor), we performed separate one-sided paired t-tests comparing the log-transformed tremor amplitudes between sessions (placebo vs. propranolol). We performed separate t-tests per tremor type because not all patients had all three types of tremor. We did the same analysis with tremor frequency as dependent variable. For one patient, tremor amplitude could not be compared due to technical issues, so for this patient only tremor frequency was compared between sessions.

Subject analysis set title	Effects of propranolol during the fMRI task
Subject analysis set type	Per protocol

Subject analysis set description:

Clinical effects during functional MRI: To assess whether the task indeed activated the noradrenergic system during coco blocks, we calculated the average time course across subjects for tremor amplitude (accelerometry), heart rate and pupil diameter. We then performed two-way repeated measures ANOVAs for these measures with two within-subject factors TRIAL (rest vs. coco) and DRUG (propranolol vs. placebo).
Cerebral effects: First-level contrasts were entered into our second-level analysis, which consisted of a two-way repeated measures ANOVAs for effects of factors TRIAL (rest vs. coco) and DRUG (propranolol vs. placebo) on both task-related and tremor-related brain activity. For analysis of task-related activity, we performed a whole brain search. Given our a-priori hypothesis on involvement of the cerebello-

thalamo-cortical circuit in PD tremor, we focused our analysis on tremor-related activity on the regions within this circuit, using small volume correction.

Reporting group values	Clinical effects of propranolol on different PD tremor types	Effects of propranolol during the fMRI task	
Number of subjects	27	23	
Age categorical Units: Subjects			
Adults (18-64 years)	17	14	
From 65-84 years	10	9	
Age continuous Units: years			
arithmetic mean	61	62	
full range (min-max)	46 to 72	49 to 72	
Gender categorical Units: Subjects			
Female	9	7	
Male	18	16	
Disease duration Units: years			
arithmetic mean	4.2	4.2	
standard deviation	± 2.9	± 2.9	

End points

End points reporting groups

Reporting group title	Tremor-dominant group

Reporting group description:

27 participants passed all screening and pre-assignment. This means that these 27 patients received propranolol and placebo, in a cross-over design, in a counterbalanced order (double blind). 24 participants completed all test procedures.

Reporting group title	Non-tremor control group

Reporting group description:

This participant group was included to compare MRI measures, but did not receive any study medication.

Subject analysis set title	Clinical effects of propranolol on different PD tremor types
Subject analysis set type	Per protocol

Subject analysis set description:

To explore the effect of cognitive load as well as propranolol on resting tremor outside of the MRI context, we performed a two-way repeated measures-analysis of variance (ANOVA) with the log-transformed tremor amplitude (averaged across two repetitions per condition) as dependent variable, and the two within-subject variables TRIAL (rest vs. coco trials) and DRUG (propranolol vs. placebo session). For the remaining two tremor conditions (postural tremor and kinetic tremor), we performed separate one-sided paired t-tests comparing the log-transformed tremor amplitudes between sessions (placebo vs. propranolol). We performed separate t-tests per tremor type because not all patients had all three types of tremor. We did the same analysis with tremor frequency as dependent variable. For one patient, tremor amplitude could not be compared due to technical issues, so for this patient only tremor frequency was compared between sessions.

Subject analysis set title	Effects of propranolol during the fMRI task
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Subject analysis set description:

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Cerebral effects: First-level contrasts were entered into our second-level analysis, which consisted of a two-way repeated measures ANOVAs for effects of factors TRIAL (rest vs. coco) and DRUG (propranolol vs. placebo) on both task-related and tremor-related brain activity. For analysis of task-related activity, we performed a whole brain search. Given our a-priori hypothesis on involvement of the cerebello-thalamo-cortical circuit in PD tremor, we focused our analysis on tremor-related activity on the regions within this circuit, using small volume correction.

Primary: Tremor

End point title	Tremor[1]

End point description:

End point type	Primary

End point timeframe:

Difference between propranolol and placebo session

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: That is because there are not two different groups receiving the drug and placebo: our study has a cross-over design. However, this system gives an error if less than two groups are selected so I had to select two groups that are practically the same people. All 27 tremor-dominant participants receive both propranolol and placebo on a different day. What I report is a comparison between tremor power between propranolol and placebo session.

End point values	Tremor-dominant group	Clinical effects of propranolol on different PD tremor types	Effects of propranolol during the fMRI task	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	27[2]	27	23	
Units: Power				
arithmetic mean (standard deviation)				
propranolol	9.1 (± 1.4)	9.1 (± 1.4)	7.3 (± 1.7)	
placebo	9.7 (± 1.5)	9.7 (± 1.5)	8.1 (± 2.1)	

Notes:

[2] - 27 participants received propranolol and placebo (on different days).

Attachments (see zip file)	Results tremor types/Results Tremor registration.png Results tremor during fMRI/Results Clinical effects.png

Statistical analyses

Statistical analysis title	Effect propranolol on rest tremor

Statistical analysis description:

Cognitive coactivation increased tremor (main effect TRIAL: F(1,24)=10.5; p=.003), whereas propranolol reduced tremor (main effect DRUG: F(1,24)=10.6; p=.003), but there was no TRIAL*DRUG interaction (F(1,24)=0.0; p=.95).

Comparison groups	Tremor-dominant group v Clinical effects of propranolol on different PD tremor types
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANOVA

Statistical analysis title	Effect propranolol on tremor during MRI

Statistical analysis description:

Similar to measurements outside the scanner, cognitive coactivation increased tremor amplitude (main effect TRIAL: F(1,19)=13.8; p=.001), while propranolol reduced tremor amplitude (main effect DRUG: F(1,19)=6.4; p=.02); no TRIAL*DRUG interaction (F(1,19)=0.7; p=.41).

Comparison groups	Tremor-dominant group v Effects of propranolol during the fMRI task
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	ANOVA

Primary: Tremor-related brain activity

End point title	Tremor-related brain activity[3]

End point description:

End point type	Primary

End point timeframe:

Difference between propranolol and placebo session

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: That is because there are not two different groups receiving the drug and placebo: our study has a cross-over design. However, this system gives an error if less than two groups are selected so I had to select two groups that are practically the same people. All 27 tremor-dominant participants receive both propranolol and placebo on a different day. What I report is a comparison between tremor-related activity between propranolol and placebo session.

End point values	Tremor-dominant group	Effects of propranolol during the fMRI task		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	23[4]	23		
Units: BOLD signal				
number (not applicable)	0	0		

Notes:

[4] - 24 completed all test procedures, for N=1 there were technical issues so N=23 included in analysis

Statistical analyses

Statistical analysis title	functional MRI analysis

Statistical analysis description:

There was no TRIAL*DRUG interaction and no main effect of TRIAL for tremor-related activity in either of the regions in the cerebello-thalamo-cortical circuit. Propranolol reduced tremor-related activity in the motor cortex across the two sessions (main effect DRUG: t(22)=2.2; p=.02). In the cerebellum, the effect of propranolol approached significance (main effect DRUG: t(22)=1.7; p=.06). There was no effect on tremor-related activity in the thalamus (VLpv; main effect DRUG: t(22)=0.15; p=.44).

Comparison groups	Tremor-dominant group v Effects of propranolol during the fMRI task
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	t-test, 2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events have been assessed during the whole period of data collection, namely between October 31, 2019 and September 6, 2021.

Adverse event reporting additional description:

In case of suspected occurrence of an AE during the testing day, the investigator interviewed the participant to inquire any adverse symptoms. AEs were reported in data management system Castor. All AEs were followed until they were abated or stabilized. Depending on the event, follow up could include referral to the general physician.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	Propranolol 40 mg oral

Reporting group description: -

Serious adverse events	Propranolol 40 mg oral		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Propranolol 40 mg oral		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 27 (11.11%)		
Nervous system disorders			
Dizziness	Additional description: One patient experienced dizziness and got anxious because of that. Therefore, she could not complete the whole MRI protocol.		
subjects affected / exposed	1 / 27 (3.70%)		
occurrences (all)	2		
Pain in extremity	Additional description: Two subjects reported pain during the testing day. This could be either related to not taking their regular PD medication, or to the intensive testing day, or it could be unrelated to the study.		
subjects affected / exposed	2 / 27 (7.41%)		
occurrences (all)	2		

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