Clinical trial results:
Early-life stress, the endocannabinoid system, and fear memory extinction

Summary

EudraCT number	2017-004823-66
Trial protocol	NL
Global end of trial date	08 July 2021

Results information

Result version number	v1 (current)
This version publication date	16 July 2022
First version publication date	16 July 2022

Trial information

Trial identification

Sponsor protocol code	NL62274.091.17

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Radboud university medical center
Sponsor organisation address	P.O. Box 9101, Nijmegen, Netherlands, 6500 HB
Public contact	Dept Psychiatry Radboudumc, Radboudumc, +31 243613490, robbert-jan.verkes@radboudumc.nl
Scientific contact	Dept Psychiatry Radboudumc, Radboudumc, +31 243613490, robbert-jan.verkes@radboudumc.nl

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	08 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 July 2021
Global end of trial reached?	Yes
Global end of trial date	08 July 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Primary objective: Our key objective is to determine if glucocorticoid administration and/or THC administration facilitates fear memory extinction retention in an experimental model of exposure therapy in healthy individuals with early life stress.

Protection of trial subjects:

After every screening session and at each end of the experimental session, we will conclude with a structured interview in which we will ask participants if they experience emotional disturbances triggered by the questions (e.g., regarding early-life trauma), at that moment or later, we can redirect them for additional help if needed. When participants are excluded from participation, we will carefully explain to them the reason for exclusion.

Background therapy:

n.a.

Evidence for comparator:

n.a.

Actual start date of recruitment	03 October 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: 54
Worldwide total number of subjects	54
EEA total number of subjects	54

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)	54

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment started on 03-10-2019 to 08-07-2021 and was in The Netherlands.

Pre-assignment

Screening details:

Healthy adults aged between 18-45 yrs old, gender-mixed, no illness, and current treatment. Participant were selected based presence or absence of a history of childhood trauma.

Period 1

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

Blinding implementation details:

Both participants and researchers are blinded from the information of randomization .

Arms

Are arms mutually exclusive?	Yes
Arm title	Childhood trauma group

Arm description:

The participants were assigned to the traumatized group.

Arm type	Experimental
Investigational medicinal product name	Hydrocortisone
Investigational medicinal product code	RVG 50730
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

20mg hydrocortisone dissolved in juice.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

20mg undistinguishable placebo (cellulose) dispersed in juice.

Arm title	Control group

Arm description:

The participants assigned to control group

Arm type	Experimental
Investigational medicinal product name	Hydrocortisone
Investigational medicinal product code	RVG 50730
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

20mg hydrocortisone dispersed in the juice allowing affordable blinding of the study participants from treatment.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

20mg undistinguishable placebo dispersed in the juice allowing affordable blinding of the study participants from treatment.

Number of subjects in period 1	Childhood trauma group	Control group
Started	27	27
Data collection finished	27	27
Completed	27	27

Baseline characteristics

Reporting groups

Reporting group title	Data collection

Reporting group description: -

Reporting group values	Data collection	Total	
Number of subjects	54	54	
Age categorical			
There should be no differences of age between groups (with and without ELS)			
Units: Subjects			
Adults (18-64 years)	54	54	
Gender categorical			
Gender was relatively balanced between groups (with and without ELS).			
Units: Subjects			
Female	32	32	
Male	22	22	

Subject analysis sets

Subject analysis set title	Drug effect on fear extinction retention
Subject analysis set type	Full analysis

Subject analysis set description:

The raw physiological data were converted and analyzed with an in-house tool in matlab. A repeated measures ANOVA was applied as a statistical model to check if the effect of hydrocortisone on fear extinction retention was equal or not in the traumatized group compared to control group.

Subject analysis set title	Drug effect on neural activity to autobiographical memory
Subject analysis set type	Full analysis

Subject analysis set description:

To determine the effect of hydrocortisone on neural activity during emotional memory recall in the traumatized vs. control groups. The (functional) MRI data was preprocessed and analyzed in matlab 2021.

Reporting group values	Drug effect on fear extinction retention	Drug effect on neural activity to autobiographical memory	
Number of subjects	52	50	
Age categorical			
There should be no differences of age between groups (with and without ELS)			
Units: Subjects			
Adults (18-64 years)	52	50	
Gender categorical			
Gender was relatively balanced between groups (with and without ELS).			
Units: Subjects			
Female	31	30	
Male	21	20	

End points

End points reporting groups

Reporting group title	Childhood trauma group

Reporting group description:

The participants were assigned to the traumatized group.

Reporting group title	Control group

Reporting group description:

The participants assigned to control group

Subject analysis set title	Drug effect on fear extinction retention
Subject analysis set type	Full analysis

Subject analysis set description:

The raw physiological data were converted and analyzed with an in-house tool in matlab. A repeated measures ANOVA was applied as a statistical model to check if the effect of hydrocortisone on fear extinction retention was equal or not in the traumatized group compared to control group.

Subject analysis set title	Drug effect on neural activity to autobiographical memory
Subject analysis set type	Full analysis

Subject analysis set description:

To determine the effect of hydrocortisone on neural activity during emotional memory recall in the traumatized vs. control groups. The (functional) MRI data was preprocessed and analyzed in matlab 2021.

Primary: Autonomic nervous system indices of the fear response and its recovery after extinction.

End point title	Autonomic nervous system indices of the fear response and its recovery after extinction.

End point description:

Our primary endpoint is retention of safety learning in an experimental model of exposure therapy. This measure is operationalized as the magnitude of spontaneous recovery of differential autonomic nervous system reactivity (primarily indexed by skin conductance responses) to fear-conditioned stimuli (vs. control stimuli) one day after extinction (i.e., safety learning).

End point type	Primary

End point timeframe:

Primary endpoint is measured 24 hrs after administration of the drug to assess drug effects on retention of safety learning.

End point values	Childhood trauma group	Control group	Drug effect on fear extinction retention	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	25	27[1]	52	
Units: Skin conductance response magnitude				
arithmetic mean (standard error)	-.20 (± .13)	.084 (± .17)	-.058 (± .11)	

Notes:

[1] - data for two participants was lost due to technical failure

Statistical analyses

Statistical analysis title	Between-group comparison of drug effect

Statistical analysis description:

Preliminary analysis of the difference in effect of hydrocortisone on retention of extinction memory in the childhood trauma versus control group

Comparison groups	Childhood trauma group v Control group
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.2
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.72
Variability estimate	Standard error of the mean
Dispersion value	0.22

Notes:

[2] - Test of an experimental effect.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From 03-10-2019 to 08-07-2021, there were adverse events involving four participants.

Adverse event reporting additional description:

Four adverse events were reported by participants. All procedures were terminated upon adverse events. Investigators followed standard procedures such as calming down and monitoring the participant, and following up the next day.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Childhood trauma group

Reporting group description:

These are healthy volunteer participants selected for history of childhood trauma.

Reporting group title	Non-trauma control group

Reporting group description:

These are healthy volunteer participants selected for absence of a history of childhoof trauma.

Serious adverse events	Childhood trauma group	Non-trauma control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Childhood trauma group	Non-trauma control group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 27 (7.41%)	2 / 27 (7.41%)	
Nervous system disorders			
Migraine	Additional description: Participant complained of headache/migraine and therefore terminated participation in an MRI scan.		
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences (all)	1	0	
Vertigo	Additional description: One participant reported dizziness during blood sampling.		
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	

Social circumstances			
Pain	Additional description: As part of procedures, participant received mild electrical shock to the fingers. One participant reported discomfort during this procedure.		
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	
occurrences (all)	0	1	
Claustrophobia	Additional description: One participant reported discomfort during MRI scanning because of confinement.		
subjects affected / exposed	1 / 27 (3.70%)	0 / 27 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2019	Due to a substantial delay in the production of one of the study medications used in our study (THC tablets, produced by Echo Pharmaceuticals), we have decided to split our three-armed study design (placebo, hydrocortisone, THC) into two two-armed substudies (hydrocortisone versus placebo, THC versus placebo). This will allow us to start data acquisition for the hydrocortisone versus placebo substudy while waiting for the release of the THC tablets.
08 July 2021	The study was ended in May 2022 due to continuing delays in the production of one of the study medications used in our study (THC tablets, produced by Echo Pharmaceuticals). Therefore, only one of the two substudies (hydrocortisone versus placebo) has been completed, while the second substudy (THC versus placebo) cannot be conducted anymore.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 March 2020	Due to the COVID-19 pandemic, we had to halt the study for 4 months.	06 July 2020

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the delay of THC providing, we split up the 2*3 study into two 2*2 substudies, namely there was no direct comparison between the effect of Hydrocortisone and THC on fear recall retention and relevant central neural activity.

Notes: