Clinical trial results:
Looking into the eye of ADHD. Investigating the relationship between ADHD, the delayed circadian rhythm and the functioning of the eye.

Summary

EudraCT number	2013-005017-12
Trial protocol	NL
Global end of trial date	10 May 2021

Results information

Result version number	v1 (current)
This version publication date	12 June 2022
First version publication date	12 June 2022

Trial information

Trial identification

Sponsor protocol code	EyeADHD03

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Nederlands Trail Register: NL4187 / NTR4337

Notes:

Sponsors

Sponsor organisation name	Parnassia Group
Sponsor organisation address	Monsterseweg 93, Den Haag, Netherlands, 2553 RJ
Public contact	MN Böhmer, Parnassia Groep / PsyQ Haaglanden, +31 0883570126, m.bohmer@parnassiagroep.nl
Scientific contact	MN Böhmer, Parnassia Groep / PsyQ Haaglanden, +31 0883570126, m.bohmer@parnassiagroep.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	18 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 May 2021
Global end of trial reached?	Yes
Global end of trial date	10 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this project is to investigate associations between visual system functioning, ADHD, and the circadian rhythm. We will also investigate the effects on the functioning of the visual system of commonly used treatments for ADHD and related disorders: methylphenidate, light therapy, and melatonin. In case we find visual system deficiencies that are specific to ADHD, the development of an objective diagnostic test for ADHD will come closer.

List of objectives:
- To determine the prevalence and type of visual system deficiencies in adults with ADHD and in healthy controls.
- To study the relationship between visual system deficiencies, ADHD symptoms, circadian rhythm, and comorbid psychiatric disorders.
- To evaluate the single-dose effect of methylphenidate, melatonin and bright light on the visual system functioning in adults with ADHD.
- To evaluate the effect of a 3-week treatment with these agents on the visual system functioning in adults with ADHD.

Protection of trial subjects:

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

Background therapy:

(i) Methylphenidate (Mph):
In Phase 2: a three-week intervention period of 3 x 20 mg/day of Ritalin ® at 8 AM, 12 PM and 4 PM. Ritalin ® is registered as medicinal treatment for ADHD in children. For adults with ADHD, Mph is widely used internationally and is the first choice of treatment. Mph is a mild CNS stimulant with more prominent effects on mental than on motor activities. Its mode of action in man is not fully understood but its effects are thought to be due to an inhibition of dopamine reuptake in the striatum, without triggering the release of dopamine.

In a meta-analysis by Castells et al. (2012), the treatment discontinuation of methylphenidate was studied in 2,496 adult patients from 12 studies. The authors conclude that treatment was more discontinuated in methylphenidate than in placebo due to adverse events. Methylphenidate was more effective for the reduction of ADHD symptoms than placebo.

(ii) Light Therapy (LT):
In Phase 2: a three-week intervention period of 30 minutes/day of LT in the morning between 7 and 10 AM.
LT is effective in the treatment of seasonal affective disorder (Golden et al., 2005; Martensson, Pettersson, Berglund, & Ekselius, 2015) and to phase-shift the sleep-wake cycle (Danielsson, Jansson-Frojmark, Broman, & Markstrom, 2016; Gradisar et al., 2011)
The phase shift hypothesis states that a delayed circadian pacemaker plays an important role in SAD, and that morning LT decreases SAD symptoms by generating a phase advance (Lewy, 2009). However, the anti-depressant effect of LT in SAD is not necessarily related to a phase advance of the circadian rhythm (Burgess, Fogg, Young, & Eastman, 2004; Knapen, Gordijn, & Meesters, 2016), whereas the decrease in ADHD severity was (Rybak, McNeely, Mackenzie, Jain, & Levitan, 2006).

Evidence for comparator:

Comparator
In Phase 2, a placebo will be used as a comparator for Methylphenidate. For the Light Therapy intervention, no comparator will be used but a waiting list.

Actual start date of recruitment	01 February 2015
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: 95
Worldwide total number of subjects	95
EEA total number of subjects	95

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)	95
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients will be recruited consecutively after standard diagnostic assessment from our outpatient adult ADHD clinic at PsyQ from the Hague. The age- and sex-matched healthy controls will be recruited via the patients using the 'snowball' sampling method, or if not available, via our own personal network.

Pre-assignment

Screening details:

Inclusion criteria
Participants in Phase 1: ADHD patients and age- (+/- 5 years) and sex-matched healthy controls will participate. All participants will be aged between 18 to 40 years.
Participants Phase 2: ADHD patients with refractive errors and/or oversensitivity to light. All participants will be aged between 18 to 40 years.

Period 1

Period 1 title	Phase 1 - Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

no blinding was applicable

Arms

Are arms mutually exclusive?	Yes
Arm title	ADHD

Arm description:

ADHD patients

Arm type	Experimental
Investigational medicinal product name	Methylphenidate, immediate-release
Investigational medicinal product code	
Other name	Ritalin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ritalin will be administered as 3 x 20 mg daily, at 8 AM, 12 PM and 4 PM, thus a total daily dosage of 60 mg.

Investigational medicinal product name	Placebo-MPH
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo-MPH will be administered as 3 x 1 tablet daily, at 8 AM, 12 PM and 4 PM.

Investigational medicinal product name	Light Therapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Lozenge
Routes of administration	Unknown use

Dosage and administration details:

The LT group used the Philips Energy Lightbox® Type HF3308/01 at home, which produces light with an intensity of 10,000 lux at 20 cm distance of the eyes from the light source. Participants were instructed to use the Lightbox at 20 cm from the eyes without glasses or contact lenses, every morning between 7:00h and 9:00h for 30 minutes. The first LT session was in the presence of the researcher to instruct

participants how to correctly administer LT. The LT group filled in a log with their start and end times of every LT session. Participants received daily text messages 10 minutes before the latest possible start time as a reminder for a light therapy session. During weekly telephone appointments with the researchers, compliance was encouraged, the instructions for LT were repeated, and side-effects were evaluated. Due to obligatory COVID-19 restrictions from the Dutch government in 2020, the T2 test days for 2 participants in the light therapy group had to be delayed for a week. T

Arm title	Controls
Arm description: Sex and Age-matched Controls	
Arm type	controls
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	ADHD	Controls
Started	51	44
Baseline measurement	51	44
Completed	30	44
Not completed	21	0
not eligible for treatment	21	-

Baseline characteristics

Reporting groups	
Reporting group title	ADHD
Reporting group description:	
ADHD patients	
Reporting group title	Controls
Reporting group description:	
Sex and Age-matched Controls	

Reporting group values	ADHD	Controls	Total
Number of subjects	51	44	95
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age			
Units: years			
arithmetic mean	26.51	27.50	
standard deviation	± 5.00	± 5.67	-
Gender categorical			
Units: Subjects			
Female	30	25	55
Male	21	19	40
ADHD-RS adulthood			
total score on ADHD-RS adulthood			
Units: points			
arithmetic mean	32.98	8.93	
standard deviation	± 7.24	± 5.53	-

End points

End points reporting groups

Reporting group title	ADHD
Reporting group description: ADHD patients	
Reporting group title	Controls
Reporting group description: Sex and Age-matched Controls	
Subject analysis set title	ADHDplac
Subject analysis set type	Per protocol
Subject analysis set description: The effect of treatment (PLAC vs MEP vs LT) in ADHD	
Subject analysis set title	ADHDlt
Subject analysis set type	Per protocol
Subject analysis set description: ADHD patients who received LT	
Subject analysis set title	ADHDmph
Subject analysis set type	Per protocol
Subject analysis set description: ADHD patients who received methylphenidate	

Primary: Pipr

End point title	Pipr
End point description:	
End point type	Primary
End point timeframe: Pipr at T0 for ADHD-controls and Pips at T1 after 3 weeks of treatment in ADHD patients	

End point values	ADHD	Controls	ADHDplac	ADHDlt
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	51	44	10[1]	10
Units: mm				
arithmetic mean (standard deviation)	1.99 (± .88)	2.20 (± 1.08)	2.6 (± .97)	1.66 (± .54)

Notes:
[1] - ADHD_plac

End point values	ADHDmph			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: mm				
arithmetic mean (standard deviation)	2.23 (± 1.11)			

Statistical analyses

Statistical analysis title	Comparison ADHD-controls analysis

Statistical analysis description:

Independent t-tests and ANOVAs were used explore any differences in general characteristics between ADHD patients and controls.

Comparison groups	ADHD v Controls
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	t-test, 2-sided

Statistical analysis title	ADHD comparison treatment

Statistical analysis description:

For Phase 2, ANOVAs were used explore any differences in general characteristics and ADHD-RS between the three interventions (light therapy, methylphenidate and placebo), and compared between T0 and T2. The effects of the three interventions on PIPS outcomes at T2 were compared using linear mixed models with corrected for baseline T0 values of the PIPR outcomes,

Comparison groups	ADHDplac v ADHDlt v ADHDmph
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05
Method	Mixed models analysis
Variability estimate	Standard deviation

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The sponsor will report the SAEs through the web portal ToetsingOnline to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse events.

Assessment type	Non-systematic

Dictionary used

Dictionary name	WMO
Dictionary version	10.1

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

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: No adverse events occured during this study

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
13 March 2020	Global covid-pandemic	13 August 2020

Notes:

Limitations and caveats

None reported