Clinical trial results:
Genetic modulation of functional brain activity of attention-deficit/hyperactivity disorder-related working memory processes

Summary

EudraCT number	2008-006242-26
Trial protocol	DE
Global end of trial date	23 October 2013

Results information

Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019

Trial information

Trial identification

Sponsor protocol code	W004PS0108 2.0

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01351272
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Würzburg
Sponsor organisation address	Josef-Schneider-Str. 2, Würzburg, Germany, 97080
Public contact	Prof. Dr. Jürgen Deckert, Klinik für Psychiatrie, Psychosomatik und Psychotherapie, 0049 93120177000, Deckert_J@ukw.de
Scientific contact	Prof. Dr. Martin Herrmann, Klinik für Psychiatrie, Psychosomatik und Psychotherapie, 0049 93120176650, Herrmann_m@ukw.de

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	31 December 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2012
Global end of trial reached?	Yes
Global end of trial date	23 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1: To examine the modulation of the functional brain activity during working memory processes by therapeutic methylphenidate administration in ADHD patients
2: To examine the clinical improvement of ADHD symptoms and general functioning by therapeutic methylphenidate administration in ADHD patients

Protection of trial subjects:

Patients were seen at least two-weekly by a psychiatrist, including an interview with a review of symptoms and side effects, completion of the Clinical Global Impression (CGI) scale and completion of a standardised Side Effects Rating Scale for psychostimulants (SERS). Once a year (starting with the date of the first authorisation by the competent authority) throughout the trial a safety report according to § 13 (6) GCP-V and "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, Rev. 2, April 2006" has been submitted to the competent authority and the Ethics Committee.

Background therapy:

none

Evidence for comparator:

The treatment with the stimulant methylphenidate has a clinical effect in children, adolescent and adults with ADHD (Smith et al., 2000; Schachter et al., 2001; Faraone et al., 2004) and is therefore the first-line treatment for ADHD. The therapeutic administration of MPH in ADHD patients over four weeks seems to improve response inhibition as well as working memory task performance (Coghill et al., 2007) and recognition memory (Rhodes et al., 2004). A recent positron emission tomography (PET) study (Schweitzer et al., 2004) showed that optimal therapeutic administration of MPH over three weeks improves the working memory performance of ADHD patients and reduces the rCBF in the prefrontal cortex. In an randomized, placebo-controlled study over 6 weeks (Bush et al., 2008) a normalisation of the dorsal anterior midcingulate cortex activity during an Multi-Source Interference Task in the methylphenidate group has been found.

Actual start date of recruitment	05 April 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	41
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of clinical trial start: 05.04.2011 (first visit of first patient (FVFP))
Date of last patient: 10/2012

Pre-assignment

Screening details:

The proposed study was conducted in a group of patients with Attention-Deficit/Hyperactivity Disorder (ADHD) (DSM-IV diagnoses: 314.xx), who were admitted to psychiatric out- or inpatient treatment at the University Hospital of Würzburg, Department of Psychiatry, Psychosomatics and Psychotherapy.

Pre-assignment period milestones

Number of subjects started	41
Number of subjects completed	35

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 6

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo administration
Within this double blind study the same procedure as described for Methylphenidat-HCl was applied for the placebo condition.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	o
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Within this double blind study the same procedure as described for Methylphenidat-HCl was applied for the placebo condition.

Arm title	Methylphenidate, non-retard

Arm description:

Drug: Methylphenidate, non-retard
Medication (methylphenidate, non-retard) will be titrated to optimal response within 6 weeks, with a maximum of 10 mg/day in week 1, 20 mg/day in week 2, 30 mg/day in week 3, 40 mg/day in week 4, 50 mg/day in week 5, and 60 mg/day in week 6, unless adverse effects emerged. After successful adjustment, medication will be maintained until week 6. Dosing will be based on at least two-weekly evaluations by a psychiatrist, including an interview with a review of symptoms and side effects, completion of the Clinical Global Impression (CGI) scale and completion of a standardised Side Effects Rating Scale for psychostimulants (SERS). The maximal daily dosage of MPH is 60 mg.

Arm type	Experimental
Investigational medicinal product name	Methylphenidat-HCl
Investigational medicinal product code	N06BA04
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Medication (methylphenidate, non-retard) will be titrated to optimal response within 6 weeks, with a maximum of 10 mg/day in week 1, 20 mg/day in week 2, 30 mg/day in week 3, 40 mg/day in week 4, 50 mg/day in week 5, and 60 mg/day in week 6, unless adverse effects emerged. After successful adjustment, medication will be maintained until week 6. Dosing will be based on at least two-weekly evaluations by a psychiatrist, including an interview with a review of symptoms and side effects, completion of the Clinical Global Impression (CGI) scale and completion of a standardised Side Effects Rating Scale for psychostimulants (SERS). The maximal daily dosage of MPH is 60 mg.

Number of subjects in period 1[1]	Placebo	Methylphenidate, non-retard
Started	16	19
Completed	16	19

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: 6 patients were excluded out after informed consent were given

Period 2

Period 2 title	postfMRI
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo administration
Within this double blind study the same procedure as described for Methylphenidat-HCl was applied for the placebo condition.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Medication (methylphenidate, non-retard) will be titrated to optimal response within 6 weeks, with a maximum of 10 mg/day in week 1, 20 mg/day in week 2, 30 mg/day in week 3, 40 mg/day in week 4, 50 mg/day in week 5, and 60 mg/day in week 6, unless adverse effects emerged. After successful adjustment, medication will be maintained until week 6. Dosing will be based on at least two-weekly evaluations by a psychiatrist, including an interview with a review of symptoms and side effects,

completion of the Clinical Global Impression (CGI) scale and completion of a standardised Side Effects Rating Scale for psychostimulants (SERS). The maximal daily dosage of MPH is 60 mg.

Arm title	Methylphenidate, non-retard

Arm description:

Drug: Methylphenidate, non-retard
Medication (methylphenidate, non-retard) will be titrated to optimal response within 6 weeks, with a maximum of 10 mg/day in week 1, 20 mg/day in week 2, 30 mg/day in week 3, 40 mg/day in week 4, 50 mg/day in week 5, and 60 mg/day in week 6, unless adverse effects emerged. After successful adjustment, medication will be maintained until week 6. Dosing will be based on at least two-weekly evaluations by a psychiatrist, including an interview with a review of symptoms and side effects, completion of the Clinical Global Impression (CGI) scale and completion of a standardised Side Effects Rating Scale for psychostimulants (SERS). The maximal daily dosage of MPH is 60 mg.

Arm type	Experimental
Investigational medicinal product name	Methylphenidat-HCl
Investigational medicinal product code	N06BA04
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Medication (methylphenidate, non-retard) will be titrated to optimal response within 6 weeks, with a maximum of 10 mg/day in week 1, 20 mg/day in week 2, 30 mg/day in week 3, 40 mg/day in week 4, 50 mg/day in week 5, and 60 mg/day in week 6, unless adverse effects emerged. After successful adjustment, medication will be maintained until week 6. Dosing will be based on at least two-weekly evaluations by a psychiatrist, including an interview with a review of symptoms and side effects, completion of the Clinical Global Impression (CGI) scale and completion of a standardised Side Effects Rating Scale for psychostimulants (SERS). The maximal daily dosage of MPH is 60 mg.

Number of subjects in period 2	Placebo	Methylphenidate, non-retard
Started	16	19
Completed	13	14
Not completed	3	5
Protocol deviation	3	5

Baseline characteristics

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo administration
Within this double blind study the same procedure as described for Methylphenidat-HCl was applied for the placebo condition.

Reporting group title	Methylphenidate, non-retard

Reporting group description:

Drug: Methylphenidate, non-retard
Medication (methylphenidate, non-retard) will be titrated to optimal response within 6 weeks, with a maximum of 10 mg/day in week 1, 20 mg/day in week 2, 30 mg/day in week 3, 40 mg/day in week 4, 50 mg/day in week 5, and 60 mg/day in week 6, unless adverse effects emerged. After successful adjustment, medication will be maintained until week 6. Dosing will be based on at least two-weekly evaluations by a psychiatrist, including an interview with a review of symptoms and side effects, completion of the Clinical Global Impression (CGI) scale and completion of a standardised Side Effects Rating Scale for psychostimulants (SERS). The maximal daily dosage of MPH is 60 mg.

Reporting group values	Placebo	Methylphenidate, non-retard	Total
Number of subjects	16	19	35
Age categorical Units: Subjects			
Adults (18-64 years)	16	19	35
Age continuous Units: years			
arithmetic mean	34	37.1	
standard deviation	± 9.78	± 9.72	-
Gender categorical Units: Subjects			
Female	7	9	16
Male	9	10	19

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo administration
Within this double blind study the same procedure as described for Methylphenidat-HCl was applied for the placebo condition.

Reporting group title	Methylphenidate, non-retard

Reporting group description:

Drug: Methylphenidate, non-retard
Medication (methylphenidate, non-retard) will be titrated to optimal response within 6 weeks, with a maximum of 10 mg/day in week 1, 20 mg/day in week 2, 30 mg/day in week 3, 40 mg/day in week 4, 50 mg/day in week 5, and 60 mg/day in week 6, unless adverse effects emerged. After successful adjustment, medication will be maintained until week 6. Dosing will be based on at least two-weekly evaluations by a psychiatrist, including an interview with a review of symptoms and side effects, completion of the Clinical Global Impression (CGI) scale and completion of a standardised Side Effects Rating Scale for psychostimulants (SERS). The maximal daily dosage of MPH is 60 mg.

Reporting group title	Placebo

Reporting group description:

Placebo administration
Within this double blind study the same procedure as described for Methylphenidat-HCl was applied for the placebo condition.

Reporting group title	Methylphenidate, non-retard

Reporting group description:

Drug: Methylphenidate, non-retard
Medication (methylphenidate, non-retard) will be titrated to optimal response within 6 weeks, with a maximum of 10 mg/day in week 1, 20 mg/day in week 2, 30 mg/day in week 3, 40 mg/day in week 4, 50 mg/day in week 5, and 60 mg/day in week 6, unless adverse effects emerged. After successful adjustment, medication will be maintained until week 6. Dosing will be based on at least two-weekly evaluations by a psychiatrist, including an interview with a review of symptoms and side effects, completion of the Clinical Global Impression (CGI) scale and completion of a standardised Side Effects Rating Scale for psychostimulants (SERS). The maximal daily dosage of MPH is 60 mg.

Primary: Working memory task- 2Back misses

End point title	Working memory task- 2Back misses

End point description:

End point type	Primary

End point timeframe:

6 weeks

End point values	Placebo	Methylphenidate, non-retard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: number of missed trials				
arithmetic mean (standard deviation)	-6.41 (± 8.84)	-9.52 (± 11.27)		

Statistical analyses

Statistical analysis title	Change from pre to post treatment

Statistical analysis description:

To test whether ADHS symptoms change over time differently in verum or placebo condition we reported the changes in scores from pre to post. The statistic approach was an ANOVA and we reported the p values of the interaction effect

Comparison groups	Placebo v Methylphenidate, non-retard
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.44
Method	ANOVA
Parameter estimate	Mean difference (final values)

Secondary: Caars Inattentive

End point title	Caars Inattentive

End point description:

End point type	Secondary

End point timeframe:

6 weeks treatment

End point values	Placebo	Methylphenidate, non-retard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: Questionaire score				
arithmetic mean (standard deviation)	-8 (± 11.4)	-11.57 (± 6.97)		

Statistical analyses

Statistical analysis title	change from pre to post treatment

Statistical analysis description:

To test whether ADHS symptoms change over time differently in verum or placebo condition we reported the changes in scores from pre to post. The statistic approach was an ANOVA and we reported the p values of the interaction effect

Comparison groups	Placebo v Methylphenidate, non-retard

Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	ANOVA
Parameter estimate	Mean difference (final values)
Variability estimate	Standard deviation

Secondary: Caars hyperactive/impulsive

End point title	Caars hyperactive/impulsive

End point description:

End point type	Secondary

End point timeframe:

6 weeks treatment

End point values	Placebo	Methylphenidate, non-retard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: questionaire score				
arithmetic mean (standard deviation)	-5.92 (± 6.84)	-6.14 (± 12.02)		

Statistical analyses

Statistical analysis title	changes in score from pre to post

Statistical analysis description:

To test whether ADHS symptoms change over time differently in verum or placebo condition we reported the changes in scores from pre to post. The statistic approach was an ANOVA and we reported the p values of the interaction effect

Comparison groups	Placebo v Methylphenidate, non-retard
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.94
Method	ANOVA
Parameter estimate	Mean difference (final values)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs was collected from enrolment until the end of the study. The patients were seen every 2 weeks during treatment (4 visits within 6 weeks) and after 4 weeks at follow up.

Assessment type	Non-systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	14

Reporting groups

Reporting group title	Patients of verum group

Reporting group description:

Patients of verum group who received at least one medication

Reporting group title	Patients of placebo group

Reporting group description: -

Serious adverse events	Patients of verum group	Patients of placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Appendicitis	Additional description: Occured after inclusion, but before beginning of actual study, in particular before medication		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Patients of verum group	Patients of placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 19 (94.74%)	10 / 16 (62.50%)	
Cardiac disorders			
Labile blood pressure			
subjects affected / exposed	2 / 19 (10.53%)	0 / 16 (0.00%)	
occurrences (all)	2	0	

Palpitations			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Therapeutic apical closure			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 19 (52.63%)	4 / 16 (25.00%)	
occurrences (all)	12	4	
Ear and labyrinth disorders			
Dizziness postural			
subjects affected / exposed	1 / 19 (5.26%)	2 / 16 (12.50%)	
occurrences (all)	1	2	
Sudden hearing loss			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	0 / 19 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Infection of gastrointestinal tract			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Acid reflux			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
diarrhea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 19 (10.53%)	0 / 16 (0.00%)	
occurrences (all)	3	0	
Stomach ache			
subjects affected / exposed	1 / 19 (5.26%)	1 / 16 (6.25%)	
occurrences (all)	1	1	

Reproductive system and breast disorders			
menstrual problem			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Pain in throat			
subjects affected / exposed	2 / 19 (10.53%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Bronchitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
cough			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Feeling agitated			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Difficulty sleeping			
subjects affected / exposed	1 / 19 (5.26%)	2 / 16 (12.50%)	
occurrences (all)	3	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 19 (5.26%)	3 / 16 (18.75%)	
occurrences (all)	3	4	
cramp			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
low back pain			
subjects affected / exposed	2 / 19 (10.53%)	2 / 16 (12.50%)	
occurrences (all)	3	2	
Neck pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Tendinitis			

subjects affected / exposed	0 / 19 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
rupture of meniscus of knee			
subjects affected / exposed	0 / 19 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Infections and infestations			
common cold			
subjects affected / exposed	6 / 19 (31.58%)	1 / 16 (6.25%)	
occurrences (all)	8	1	
Herpes zoster			
subjects affected / exposed	1 / 19 (5.26%)	0 / 16 (0.00%)	
occurrences (all)	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? No

Limitations and caveats

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

We did not reach a sufficient number of patients based on the power calculation.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27207920