



## 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
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##### 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:

<b>Subjects enrolled per age group</b>	
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
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### 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
<b>Arm title</b>	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.

<b>Arm title</b>	Methylphenidate, non-retard
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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.

<b>Number of subjects in period 1<sup>[1]</sup></b>	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
<b>Arm title</b>	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.

<b>Arm title</b>	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.

<b>Number of subjects in period 2</b>	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
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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
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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
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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
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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
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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
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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
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End point description:

End point type	Primary
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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 ( $\pm$ 8.84)	-9.52 ( $\pm$ 11.27)		



## Statistical analyses

<b>Statistical analysis title</b>	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	

<b>End point values</b>	Placebo	Methylphenidate, non-retard		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	14		
Units: Questionnaire score				
arithmetic mean (standard deviation)	-8 ( $\pm$ 11.4)	-11.57 ( $\pm$ 6.97)		

## Statistical analyses

<b>Statistical analysis title</b>	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: questionnaire 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
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### Dictionary used

Dictionary name	SNOMED CT
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Dictionary version	14
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### Reporting groups

Reporting group title	Patients of verum group
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Reporting group description:

Patients of verum group who received at least one medication

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

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

subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 16 (6.25%) 1	
rupture of meniscus of knee subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	1 / 16 (6.25%) 1	
Infections and infestations common cold subjects affected / exposed occurrences (all)	6 / 19 (31.58%) 8	1 / 16 (6.25%) 1	
Herpes zoster subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 16 (0.00%) 0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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.
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Notes:

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### Online references

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