Clinical trial results:
Vigilance regulation as predictor of response to Psychostimulants in adult patients with ADHD

Summary

EudraCT number	2015-000488-15
Trial protocol	DE
Global end of trial date	16 August 2018

Results information

Result version number	v1 (current)
This version publication date	11 July 2020
First version publication date	11 July 2020

Trial information

Trial identification

Sponsor protocol code	3.0

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Leipzig
Sponsor organisation address	Ritterstr. 26, Leipzig, Germany,
Public contact	OA Dr. med. Maria Strauß, Department of Psychiatry of University of Leipzig, +49 3419724304, Maria.Strauss@medizin.uni-leipzig.de
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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	23 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 August 2018
Global end of trial reached?	Yes
Global end of trial date	16 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective of the trial is the investigation, if an unstable vigilance regulation in the EEG prior to medication (measured on VIGALL classification) predicates the response of therapy with methylphenidate in ADHD. The therapeutic target is a >30%-reduction of CAARS (CAARS-S:L - Conners' Adult ADHD Rating Scales-Self-Report: Long Version).

Protection of trial subjects:

Each patient is closely monitored with regard to safety during the course of the study. This includes, in addition to the recording of adverse events, the collection of data for each visit
the vital signs.

In addition, laboratory tests and ECG are performed before the start and at the end of the intervention.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 January 2016
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	Germany: 121
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	121
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

first patient in: 29-APR-2016;
last patient out: 16-AUG-2018
recruitment in 7 univiersity hospitals in Germany

Pre-assignment

Screening details:

- outpatients with clinically defined ADHD according to the DSM-IV were recruited at the ADHD outpatient clinic for adults
- diagnoses were confirmed by a psychiatrist and psychologist based on mental status examination, clinical history, structured clinical interviews and rating scales/questionnaires

Period 1

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

Arms

Arm title	methylphenidate

Arm description:

all patients received methylphenidate

Arm type	Experimental
Investigational medicinal product name	Methylphenidate
Investigational medicinal product code	
Other name	Medikinet adult (10 mg, 20 mg, 30 mg, 40 mg)
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

- 20 mg as an initial dose (all patients)
- dose increased each week by 20 mg/day up to a target dose
- target dose depended on body weight: 40 mg daily (weight< 55 kg) / 60 mg daily (weight 55-69 kg) / 80 mg daily (weight>=70 kg) over a course of up to 4 weeks.
- after titration target dose continued for 4 weeks.

Number of subjects in period 1	methylphenidate
Started	121
Completed	112
Not completed	9
Baseline EEG unavailable	6
Baseline CAARS unavailable	3

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	121	121	
Age categorical Units: Subjects			
Adults (18-64 years)	121	121	
Gender categorical Units: Subjects			
Female	40	40	
Male	81	81	

Subject analysis sets

Subject analysis set title	Full analysis set unstable
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects registered and who provided valid baseline EEG and CAARS data and showed unstable brain arousal

Subject analysis set title	Full analysis set stable
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects registered and who provided valid baseline EEG and CAARS data and showed stable brain arousal

Reporting group values	Full analysis set unstable	Full analysis set stable	
Number of subjects	52	60	
Age categorical Units: Subjects			
Adults (18-64 years)	52	60	
Gender categorical Units: Subjects			
Female	14	23	
Male	38	37	

End points

End points reporting groups

Reporting group title	methylphenidate
Reporting group description: all patients received methylphenidate	
Subject analysis set title	Full analysis set unstable
Subject analysis set type	Full analysis
Subject analysis set description: All subjects registered and who provided valid baseline EEG and CAARS data and showed unstable brain arousal	
Subject analysis set title	Full analysis set stable
Subject analysis set type	Full analysis
Subject analysis set description: All subjects registered and who provided valid baseline EEG and CAARS data and showed stable brain arousal	

Primary: association between brain arousal regulation and success of the therapy

End point title	association between brain arousal regulation and success of the therapy
End point description: The primary endpoint is the association between brain arousal regulation and success of the therapy. Brain arousal regulation is based on the Vigilance Algorithm Leipzig (VIGALL 2.1) and categorized to be stable or unstable based on the arousal stability score, also call the "Labilitätsindex" (Strauß et al. 2018). Scores 1–5 are considered "unstable" and 6–11 stable. Success of the therapy is defined as a >30% reduction in the total CAARS-S:L T-score from the "DSM-ADHS" 4 weeks after the titration phase compared to the baseline value.	
End point type	Primary
End point timeframe: 4 weeks after the titration phase	

End point values	methylphenidate	Full analysis set unstable	Full analysis set stable	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	121	52	60	
Units: patients	121	52	60	

Statistical analyses

Statistical analysis title	primary end point analysis
Comparison groups	Full analysis set unstable v Full analysis set stable
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	29

Adverse events

Adverse events information

Timeframe for reporting adverse events:

from the start time of the first administration of the IMP until the final visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	overall adverse events

Reporting group description: -

Serious adverse events	overall adverse events		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 121 (1.65%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 121 (0.83%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	overall adverse events		
Total subjects affected by non-serious adverse events subjects affected / exposed	80 / 121 (66.12%)		
Cardiac disorders Heart racing subjects affected / exposed occurrences (all)	5 / 121 (4.13%) 8		
Tachycardia subjects affected / exposed occurrences (all)	5 / 121 (4.13%) 6		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	19 / 121 (15.70%) 23		
Vertigo subjects affected / exposed occurrences (all)	6 / 121 (4.96%) 6		
Gastrointestinal disorders Dry mouth subjects affected / exposed occurrences (all)	10 / 121 (8.26%) 14		
Nausea subjects affected / exposed occurrences (all)	5 / 121 (4.13%) 6		
Vomiting subjects affected / exposed occurrences (all)	3 / 121 (2.48%) 5		
Psychiatric disorders Restlessness subjects affected / exposed occurrences (all)	12 / 121 (9.92%) 13		
Sleep disorder subjects affected / exposed occurrences (all)	7 / 121 (5.79%) 8		
Metabolism and nutrition disorders Decreased appetite			

subjects affected / exposed occurrences (all)	8 / 121 (6.61%) 8		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2015	Amendment 1 before start of recruitment: specification of inclusion and exclusion criteria, specification of concomitant medication
13 November 2017	extension of recruitment period; changes in SmPC

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported