



## 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 |
| Scientific contact           | OA Dr. med. Maria Strauß, Department of Psychiatry of University of Leipzig, +49 3419724304, Maria.Strauss@medizin.uni-leipzig.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                       | 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 university 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<br>Units: Subjects    |               |       |  |
| Adults (18-64 years)                  | 121           | 121   |  |
| Gender categorical<br>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<br>unstable | Full analysis set<br>stable |  |
|---------------------------------------|-------------------------------|-----------------------------|--|
| Number of subjects                    | 52                            | 60                          |  |
| Age categorical<br>Units: Subjects    |                               |                             |  |
| Adults (18-64 years)                  | 52                            | 60                          |  |
| Gender categorical<br>Units: Subjects |                               |                             |  |
| Female                                | 14                            | 23                          |  |
| Male                                  | 38                            | 37                          |  |

## End points

### End points reporting groups

|   |                            |
|---|----------------------------|
| Reporting group title   | methylphenidate            |
| Reporting group description:<br>all patients received methylphenidate   |                            |
| Subject analysis set title  | Full analysis set unstable |
| Subject analysis set type   | Full analysis              |
| Subject analysis set description:<br>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:<br>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:<br>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:<br>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 %



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

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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported