# Clinical trial results:
# Proof of concept trial to evaluate the effectiveness of combined treatment with Valerian extract (Euvegal®) and Lavender oil (Lasea®) in patients suffering from inability to fall or stay asleep

## Summary

| | |
|---|---|
| EudraCT number | 2015-003265-29 |
| Trial protocol | DE |
| Global end of trial date | 14 August 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 05 January 2020 |
| First version publication date | 05 January 2020 |
| Summary attachment (see zip file) | 750598.01.003_SummaryofResultsEudraCTDatabase_2019_12_20 (750598.01.003 SummaryOfResults_EUDRA_CT_Version 1.0_ 20191220 Final_mit Schwärzung.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 750598.01.003 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Dr. Willmar Schwabe GmbH & Co. KG |
| Sponsor organisation address | Willmar-Schwabe Straße 4, Karlsruhe, Germany, 76227 |
| Public contact | Clinical Research Department, Dr. Willmar Schwabe GmbH & Co. KG, +49 7214005573, |
| Scientific contact | Clinical Research Department, Dr. Willmar Schwabe GmbH & Co. KG, +49 7214005573, |

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 | 05 September 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 August 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 August 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The objective of the trial is to assess the effectiveness of a combined treatment with Valerian extract (Euvegal®) and Lavender oil (Lasea®) in patients with inability to fall or stay asleep.

Protection of trial subjects:

Possibility to withdraw informed consent. Monitoring of adverse events and laboratory parameters.

Background therapy: -

Evidence for comparator:

Active substances contained in Synalan.

| | |
|---|---|
| Actual start date of recruitment | 30 August 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: 94 |
| Worldwide total number of subjects | 94 |
| EEA total number of subjects | 94 |

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) | 94 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

A total 175 patients were screened for eligibility. Two of these patients were re-screened due to scheduling conflicts. 32 subjects were randomized. 1 drop out subject was replaced.

### Pre-assignment

Screening details:

32 subjects were randomised to one of six treatment sequences (Silexan - Synalan - Valeriana/Silexan - Valeriana - Synalan/Synalan - Silexan - Valeriana/Synalan - Valeriana - Silexan/Valeriana - Silexan - Synalan/Valeriana - Synalan - Silexan) in a 3-period, 3-way cross-over design.

### Pre-assignment period milestones

| | |
|---|---|
| Number of subjects started | 94 |
| Number of subjects completed | 94 |

### Period 1

| | |
|---|---|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Monitor, Data analyst, Subject, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Silexan |

Arm description:

WS® 1265 1x80mg

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Silexan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

WS® 1265 1x80 mg + WS® 1014 Placebo 1x1

| | |
|---|---|
| **Arm title** | Synalan |

Arm description:

WS® 1265 1x80 mg + WS® 1014 1x500 mg

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Synalan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

WS® 1265 1x80 mg + WS® 1014 1x500mg

| **Arm title** | Valerian |
|---|---|

Arm description:

WS® 1014 1x500 mg

| Arm type | Experimental |
|---|---|
| Investigational medicinal product name | Valerian |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

WS® 1265 Placebo 1x1 + WS® 1014 1x500mg

| **Number of subjects in period 1** | Silexan | Synalan | Valerian |
|---|---|---|---|
| Started | 31 | 32 | 31 |
| Completed | 31 | 31 | 31 |
| Not completed | 0 | 1 | 0 |
| Adverse event, non-fatal | - | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Silexan |
| Reporting group description: WS® 1265 1x80mg | |
| Reporting group title | Synalan |
| Reporting group description: WS® 1265 1x80 mg + WS® 1014 1x500 mg | |
| Reporting group title | Valerian |
| Reporting group description: WS® 1014 1x500 mg | |

| Reporting group values | Silexan | Synalan | Valerian |
|---|---|---|---|
| Number of subjects | 31 | 32 | 31 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 31 | 32 | 31 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 34.81 | 34.63 | 34.81 |
| standard deviation | ± 7.78 | ± 7.72 | ± 7.78 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 18 | 19 | 18 |
| Male | 13 | 13 | 13 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 94 | | |
| Age categorical<br>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) | 94 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 55 | | |
| Male | 39 | | |

**Subject analysis sets**

| | |
|---|---|
| Subject analysis set title | Silexan |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects, which received Silexan in period I or period II or period III.
The full analysis set (FAS) included all patients of the safety analysis who completed at least one treatment period including the Polysomnographic sleep measures (PSG) night.

| | |
|---|---|
| Subject analysis set title | Synalan |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects, which received Synalan in period I or period II or period III.
The full analysis set (FAS) included all patients of the safety analysis who completed at least one treatment period including the Polysomnographic sleep measures (PSG) night.

| | |
|---|---|
| Subject analysis set title | Valerian |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Subjects, which received Valerian in period I or period II or period III.
The full analysis set (FAS) included all patients of the safety analysis who completed at least one treatment period including the Polysomnographic sleep measures (PSG) night.

| **Reporting group values** | Silexan | Synalan | Valerian |
|---|---|---|---|
| Number of subjects | 31 | 31 | 31 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 31 | 31 | 31 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 34.81 | 34.81 | 34.81 |
| standard deviation | ± 7.78 | ± 7.78 | ± 7.78 |

| Gender categorical<br>Units: Subjects | | | |
|---|---|---|---|
| Female | 18 | 18 | 18 |
| Male | 13 | 13 | 13 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Silexan |
| Reporting group description: WS® 1265 1x80mg | |
| Reporting group title | Synalan |
| Reporting group description: WS® 1265 1x80 mg + WS® 1014 1x500 mg | |
| Reporting group title | Valerian |
| Reporting group description: WS® 1014 1x500 mg | |

| | |
|---|---|
| Subject analysis set title | Silexan |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects, which received Silexan in period I or period II or period III. The full analysis set (FAS) included all patients of the safety analysis who completed at least one treatment period including the Polysomnographic sleep measures (PSG) night. | |
| Subject analysis set title | Synalan |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects, which received Synalan in period I or period II or period III. The full analysis set (FAS) included all patients of the safety analysis who completed at least one treatment period including the Polysomnographic sleep measures (PSG) night. | |
| Subject analysis set title | Valerian |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Subjects, which received Valerian in period I or period II or period III. The full analysis set (FAS) included all patients of the safety analysis who completed at least one treatment period including the Polysomnographic sleep measures (PSG) night. | |

### Primary: Polysomnographic endpoints

| | |
|---|---|
| End point title | Polysomnographic endpoints[1] |
| End point description: This document in its section "End points" specifies commercially confidential information of Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe referred to in Article 81 Section (4) b) Regulation (EU) 536/2014 that is a trade secret and released by the holder for purposes of Regulation (EU) 536/2014 only under the condition of confidence. Trade secrets may not - even in part - be published or released to third parties other than to competent authorities without express permission of the trade secret holder. | |
| End point type | Primary |
| End point timeframe: Day 3 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: See document for a complete description of the statistical methods and results.
There were no primary end points defined for analysis. Because at least one primary end point is required to be entered study results into the database, the parameters presented here have been chosen to this purpose.

| End point values | Silexan | Synalan | Valerian | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 31 | 31 | 31 | |
| Units: minutes | | | | |
| median (inter-quartile range (Q1-Q3)) | 9999.99 (9999.99 to 9999.99) | 9999.99 (9999.99 to 9999.99) | 9999.99 (9999.99 to 9999.99) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information[1]

Timeframe for reporting adverse events:

3 Days

Adverse event reporting additional description:

5 adverse events occurred in 32 patients treated with Synalan, 1 adverse events occurred in 31 patients treated with valeriana, 1 adverse events occurred in 31 patients treated with Silexan.

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Synalan |

Reporting group description:

Synalan

| | |
|---|---|
| Reporting group title | Valeriana |

Reporting group description:

Valerian

| | |
|---|---|
| Reporting group title | Silexan |

Reporting group description:

Silexan

| Serious adverse events | Synalan | Valeriana | Silexan |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 31 (0.00%) | 0 / 31 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

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

| Non-serious adverse events | Synalan | Valeriana | Silexan |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 31 (0.00%) | 0 / 31 (0.00%) |

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: Overall, 6 of the randomized 32 subjects experienced non-serious adverse events during treatment phase. This number was not be entered into the database, because each adverse event occurred with a frequency which did not exceed the frequency threshold of 5% for reporting non-serious adverse events. Therefore, the number of subjects with non-serious adverse events resulted in 0 when considering the 5% frequency threshold.

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 25 July 2016 | The determination of the creatinine clearance was replaced by the determination of the glomerular filtration rate.<br>The allowed time for the Digit-symbol substitution test (DSST) has been prolonged from 90 to 120 seconds.<br>The use of a patient diary had not been described in the clinical trial protocol by error. Therefore, its use was added by this amendment. |
| 06 December 2016 | The time window of up to 7 days between screening visit and the polysomnography, polysomnographic sleep measures (PSG) screening nights was too short for several patients. Therefore, the period was changed to 14 days.<br>The inclusion criteria Wake-time during sleep, Total sleep time (TST) and Insomnia Severity Index (ISI) were adapted. |
| 17 March 2017 | The exclusion criterion regarding concomitant diseases was changed. |
| 30 June 2017 | The exclusion criterion regarding concomitant diseases was changed. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported