Clinical trial results:
Driving fitness under acute and subchronic application of Silexan® (WS® 1265) in comparison to placebo and Lorazepam with healthy volunteers in two successive, randomized, double-blind, crossover designed trial parts

Summary

EudraCT number	2015-001101-14
Trial protocol	DE
Global end of trial date	07 February 2018

Results information

Result version number	v1 (current)
This version publication date	17 July 2019
First version publication date	17 July 2019
Summary attachment (see zip file)	750253.01.030 Summuary of results V1.0 (750253.01.030_Zusammenfassung der Ergebnisse_mit Schwärzung_Version1.0_ 2019_07_01.pdf)

Trial information

Trial identification

Sponsor protocol code	750253.01.030

Additional study identifiers

ISRCTN number	ISRCTN32209377
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Willmar Schwabe GmbH & Co. KG
Sponsor organisation address	Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany, 76227
Public contact	Head of Clinical Research Department, Dr. Willmar Schwabe GmbH & Co. KG, +49 7214005573,
Scientific contact	Head of 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	03 August 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 July 2017
Global end of trial reached?	Yes
Global end of trial date	07 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The trial is divided in two parts. The first part of the trial is conducted in order to test the non-inferiority and equivalence, respectively, of driving fitness after acute application of 80 mg Silexan® (WS® 1265) in comparison to placebo. The second part of the trial is conducted in order to show superiority of 160 mg and 320 mg Silexan® (WS® 1265) with respect to driving fitness in comparison to 1.0 mg Lorazepam. In the second part of the trial, the comparison of 1.0 mg Lorazepam with placebo will serves to ensure the internal validity of the experimental set-up.
Driving fitness is assessed using a representative, alcohol-validated test course in a high-fidelity driving simulator.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator:

Lorazepam (Tavor, 0,5 mg, 1,0 mg, 2,0 mg and 2,5 mg) has a marketing authorisation in Germany for the symptomatic short-time treatment of anxiety, stress and agitational states as well as thereby caused sleeping disorders. It is also used as a sedative for diagnostic procedures and as a sedative pre- and aftermedication for surgery. 1 mg Lorazepam is used as the standard active drug (verum) definitely causing impairment according to the guidelines of the International Council on Alcohol, Drugs and Traffic Safety (ICADTS, 2009).

Actual start date of recruitment	04 April 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: 201
Worldwide total number of subjects	201
EEA total number of subjects	201

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	201
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First part: A total of 51 subjects were screened for eligibility. Of these, 1 subject was not included due to an adverse event. 2 drop out subjects were replaced.
Second part: A total of 25 subjects were screened for eligibility. All subjects were included. 1 drop out subject was replaced.

Pre-assignment

Screening details:

First part: 50 subjects were randomised to one of two treatment sequences (Silexan 80 mg/placebo) in a 2-period, 2-way cross-over design. Second part: 25 subjects were randomised to one of four treatment sequences (Silexan 80 mg/Silexan 160mg/Lorazepam 1mg/placebo) in a 4-period, 4-way cross-over design.

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	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Silexan 80 mg (first part)

Arm description:

WS® 1265 1x80 mg

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

Dosage and administration details:

WS® 1265 1x1

Arm title	Placebo (first part)

Arm description:

WS® 1265 Placebo 1x1

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

Dosage and administration details:

Placebo 1x1

Arm title	Silexan 160 mg (second part)

Arm description:

WS® 1265 2x80 mg + WS® 1265 Placebo 2x1 + Lorazepam Placebo 1x1

Arm type	Experimental

Investigational medicinal product name	Silexan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 purple capsules (2 Silexan® WS® 1265 + 2 Silexan® placebo) + 1 orange capsule (Lorazepam placebo)

Arm title	Silexan 320 mg (second part)

Arm description:

WS® 1265 4x80 mg + Lorazepam Placebo 1x1

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

Dosage and administration details:

4 purple capsules (Silexan® WS® 1265) + 1 orange capsule (Lorazepam placebo)

Arm title	Lorazepam 1 mg (second part)

Arm description:

WS® 1265 Placebo 4x1 + Lorazepam 1x1mg

Arm type	Experimental
Investigational medicinal product name	Lorazepam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

4 purple capsules (Silexan® placebo) + 1 orange capsule (Lorazepam verum)

Arm title	Placebo (second part)

Arm description:

WS® 1265 Placebo 4x1 + Lorazepam Placebo 1x1

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

Dosage and administration details:

4 purple capsules (Silexan® placebo) + 1 orange capsule (Lorazepam placebo)

Number of subjects in period 1[1]	Silexan 80 mg (first part)	Placebo (first part)	Silexan 160 mg (second part)
Started	50	50	25
Completed	48	48	25
Not completed	2	2	0
Pregnancy	1	1	-
schedule conflict	1	1	-

Number of subjects in period 1[1]	Silexan 320 mg (second part)	Lorazepam 1 mg (second part)	Placebo (second part)
Started	25	25	25
Completed	25	25	25
Not completed	0	0	0
Pregnancy	-	-	-
schedule conflict	-	-	-

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: In this database each sequence of a cross over trial is counting as separate study participant. The number of participants is therefore counting up to 2x50 plus 4x25, since the first part of this study has a twofold cross over design, while in the second part each participant is passing through four sequences. One participant was not included after screening, the dummy "number of subjects enrolled" is therefore adding up to 201.

Baseline characteristics

Reporting groups	
Reporting group title	Silexan 80 mg (first part)
Reporting group description:	
WS® 1265 1x80 mg	
Reporting group title	Placebo (first part)
Reporting group description:	
WS® 1265 Placebo 1x1	
Reporting group title	Silexan 160 mg (second part)
Reporting group description:	
WS® 1265 2x80 mg + WS® 1265 Placebo 2x1 + Lorazepam Placebo 1x1	
Reporting group title	Silexan 320 mg (second part)
Reporting group description:	
WS® 1265 4x80 mg + Lorazepam Placebo 1x1	
Reporting group title	Lorazepam 1 mg (second part)
Reporting group description:	
WS® 1265 Placebo 4x1 + Lorazepam 1x1mg	
Reporting group title	Placebo (second part)
Reporting group description:	
WS® 1265 Placebo 4x1 + Lorazepam Placebo 1x1	

Reporting group values	Silexan 80 mg (first part)	Placebo (first part)	Silexan 160 mg (second part)
Number of subjects	50	50	25
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)	50	50	25
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	34.2	34.2	33.1
standard deviation	± 8.90	± 8.90	± 9.77
Gender categorical Units: Subjects			
Female	23	23	14
Male	27	27	11

Reporting group values	Silexan 320 mg (second part)	Lorazepam 1 mg (second part)	Placebo (second part)
Number of subjects	25	25	25

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)	25	25	25
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	33.1	33.1	33.1
standard deviation	± 9.77	± 9.77	± 9.77
Gender categorical Units: Subjects			
Female	14	14	14
Male	11	11	11

Reporting group values	Total		
Number of subjects	200		
Age categorical 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)	200		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	102		
Male	98		

Subject analysis sets

Subject analysis set title	Silexan 80 mg (first part)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects of the first part, which received Silexan on day 1-8 or day 15-22.

Subject analysis set title	Placebo Part (first part)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects of the first part, which received placebo on day 1-8 or day 15-22.

Subject analysis set title	Silexan 160 mg (second part)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects of the second part, which received Silexan 2x80 mg on day 1, day 8, day 15 or day 22.

Subject analysis set title	Silexan 320 mg (second part)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects of the second part, which received Silexan 4x80 mg on day 1, day 8, day 15 or day 22.

Subject analysis set title	Lorazepam 1 mg (second part)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects of the second part, which received Lorazepam 1x1 mg on day 1, day 8, day 15 or day 22.

Subject analysis set title	Placebo Part (second part)
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects of the second part, which received Placebo on day 1, day 8, day 15 or day 22.

Reporting group values	Silexan 80 mg (first part)	Placebo Part (first part)	Silexan 160 mg (second part)
Number of subjects	48	48	25
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)	48	48	25
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	33.9	33.9	33.1
standard deviation	± 8.99	± 8.99	± 9.77
Gender categorical Units: Subjects			
Female	22	22	14
Male	26	26	11

Reporting group values	Silexan 320 mg (second part)	Lorazepam 1 mg (second part)	Placebo Part (second part)
Number of subjects	25	25	25

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)	25	25	25
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	33.1	33.1	33.1
standard deviation	± 9.77	± 9.77	± 9.77
Gender categorical Units: Subjects			
Female	14	14	14
Male	11	11	11

End points

End points reporting groups

Reporting group title	Silexan 80 mg (first part)
Reporting group description: WS® 1265 1x80 mg	
Reporting group title	Placebo (first part)
Reporting group description: WS® 1265 Placebo 1x1	
Reporting group title	Silexan 160 mg (second part)
Reporting group description: WS® 1265 2x80 mg + WS® 1265 Placebo 2x1 + Lorazepam Placebo 1x1	
Reporting group title	Silexan 320 mg (second part)
Reporting group description: WS® 1265 4x80 mg + Lorazepam Placebo 1x1	
Reporting group title	Lorazepam 1 mg (second part)
Reporting group description: WS® 1265 Placebo 4x1 + Lorazepam 1x1mg	
Reporting group title	Placebo (second part)
Reporting group description: WS® 1265 Placebo 4x1 + Lorazepam Placebo 1x1	
Subject analysis set title	Silexan 80 mg (first part)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects of the first part, which received Silexan on day 1-8 or day 15-22.	

Subject analysis set title	Placebo Part (first part)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects of the first part, which received placebo on day 1-8 or day 15-22.	

Subject analysis set title	Silexan 160 mg (second part)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects of the second part, which received Silexan 2x80 mg on day 1, day 8, day 15 or day 22.	

Subject analysis set title	Silexan 320 mg (second part)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects of the second part, which received Silexan 4x80 mg on day 1, day 8, day 15 or day 22.	

Subject analysis set title	Lorazepam 1 mg (second part)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects of the second part, which received Lorazepam 1x1 mg on day 1, day 8, day 15 or day 22.	

Subject analysis set title	Placebo Part (second part)
Subject analysis set type	Full analysis
Subject analysis set description: Subjects of the second part, which received Placebo on day 1, day 8, day 15 or day 22.	

Primary: Standard deviation of lane position SDLP

End point title	Standard deviation of lane position SDLP[1][2]

End point description:

Note:
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 1 and day 15

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: The reported results are chosen freely. See document for a complete description of the statistical methods and results.
Statistical analyses were conducted for the end point. Refer to the attached summary of results for details.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The reported results are chosen freely. See document for a complete description of the statistical methods and results.
Statistical analyses were conducted for the end point. Refer to the attached summary of results for details.

End point values	Silexan 80 mg (first part)	Placebo (first part)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: cm				
median (inter-quartile range (Q1-Q3))	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	
Timeframe for reporting adverse events: 9 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1
Reporting groups	
Reporting group title	No active treatment
Reporting group description: No active treatment	
Reporting group title	Lorazepam
Reporting group description: Compare medication	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Silexan
Reporting group description: Study medication	

Serious adverse events	No active treatment	Lorazepam	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 74 (0.00%)	0 / 25 (0.00%)	0 / 74 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Silexan		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 74 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	No active treatment	Lorazepam	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 74 (8.11%)	14 / 25 (56.00%)	33 / 74 (44.59%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 74 (0.00%)	3 / 25 (12.00%)	1 / 74 (1.35%)
occurrences (all)	0	3	1
Headache			
subjects affected / exposed	1 / 74 (1.35%)	1 / 25 (4.00%)	5 / 74 (6.76%)
occurrences (all)	1	1	5
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 74 (1.35%)	12 / 25 (48.00%)	22 / 74 (29.73%)
occurrences (all)	1	12	26
Gastrointestinal disorders			
Eructation			
subjects affected / exposed	0 / 74 (0.00%)	0 / 25 (0.00%)	1 / 74 (1.35%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	0 / 74 (0.00%)	0 / 25 (0.00%)	8 / 74 (10.81%)
occurrences (all)	0	0	8
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 74 (5.41%)	0 / 25 (0.00%)	1 / 74 (1.35%)
occurrences (all)	4	0	1

Non-serious adverse events	Silexan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 74 (71.62%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	7 / 74 (9.46%)		
occurrences (all)	7		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	27 / 74 (36.49%) 32		
Gastrointestinal disorders Eructation subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 37 / 74 (50.00%) 39 5 / 74 (6.76%) 5		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 2 / 74 (2.70%) 2		

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

None reported