Summary of results

Version 1.0

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

Clinical Trial No. 750253.01.030

EudraCT No. 2015-001101-14

Date of report: 01 July 2019

Trial part 1 + 2:

First subject included: 04 April 2016 (Part 1), 13 September 2016 (Part 2)

Last subject completed: 13 December 2016 (Part 1), 14 March 2017 (Part 2)

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1. Summary

Sponsor: Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany

Title of clinical trial: 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

Relevant Amendments: Not applicable – no substantial amendments

Co-ordinating investigator Not applicable (monocentric clinical trial)

Investigators: Dr. med. Klaus-Ulrich Oehler, MD

Trial sites: Medical Study Center Würzburg,
Augustinerstraße 15
97070 Würzburg, Germany

Trial period: First subject included: 04 April 2016 (Part 1), 13 September 2016 (Part 2)
Last subject completed: 13 December 2016 (Part 1), 14 March 2017 (Part 2)

Publications: None

Clinical phase: Phase IIa

Objective: The trial was divided in two parts. The first part of the trial was conducted in order to test the non-inferiority and equivalence respectively of driving fitness after acute application of 80 mg Silexan® in comparison to placebo. The second part of the trial was conducted in order to show superiority of 160 mg and 320 mg Silexan® 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 served also to ensure the internal validity of the experimental set-up.

For both study parts, driving fitness was assessed using a

representative, alcohol-validated test course in the Würzburg Institute of Traffic Sciences' (WIVW) high-fidelity driving simulator. Standard Deviation of Lane Position (SDLP) during the vigilance section in cm was chosen as the primary endpoint.

Furthermore, to evaluate a potentially different effect pattern of Silexan® as compared to placebo or Lorazepam, the following secondary endpoints were analyzed descriptively:

- Raters' global assessment of subjects' driving performance on the Fitness-to-Drive-Scale
- Number of driving errors in total and in subcategories
- Subjective assessment of driving performance on the Fitness-to-Drive-Scale
- Reaction time to sudden events
- In addition, eyelid closure index during driving was analyzed to evaluate sedation and sleepiness. Furthermore, the volunteers evaluated their sleepiness themselves by means of the Stanford Sleepiness Scale and possible adverse events were monitored.

Methodology: Part 1 of the clinical trial was conducted as a monocentric, double-blind, randomized, placebo-controlled cross-over trial with two treatments in two periods and two sequences (randomized 1:1).

Part 2 of the clinical trial was conducted as a monocentric, double-blind, randomized, placebo- and reference-controlled cross-over trial with four treatments in four periods and four sequences (randomized 1:1:1:1).

Eligible subjects participated either in trial part 1 or 2 after a screening visit. Two 8-day crossover treatment periods (with visits at day 1 (=acute application) and day 8 (=subchronic application) of the respective period) with 80 mg Silexan® per day and placebo, respectively, were separated by a wash-out period of 7 days in trial part 1. Single doses of 160 mg Silexan®, 320 mg Silexan®, 1.0 mg Lorazepam and placebo, respectively, were administered in a cross-over design with a wash-out period of each 7 days in trial part 2.

Standard deviation of lane position (SDLP) was recorded by the driving simulator. In addition, during this test a specially trained researcher registered the subjects' driving errors and assessed their driving performance. After each driving test the subjects rated their driving performance subjectively on the scale. Furthermore, reaction time to sudden events was measured by the driving simulator. In

addition, the eyelid closure index during driving was analyzed to evaluate sedation and sleepiness. Furthermore, the volunteers evaluated their sleepiness themselves by means of the Stanford Sleepiness Scale and possible adverse events were monitored.

Number of subjects included in the analysis in part 1 of the trial:

Planned to be randomized	Subjects taken into account for the analysis of				
			Safety	Efficacy	
	Screened	Randomized	Safety set (SES)	Full analysis set (FAS)	Per protocol set (PP)
Sequence "Silexan® - Placebo"		25	25	24	23
Sequence "Placebo - Silexan®"		25	25	24	23
Total	51	50	50	48	46

Number of subjects included in the analysis in part 2 of the trial:

Planned to be randomized	Subjects taken into account for the analysis of				
			Safety	Efficacy	
	Screened	Randomized	Safety set (SES)	Full analysis set (FAS)	Per protocol set (PP)
Sequence "P160320L"		7	7	7	6
Sequence "160PL320"		6	6	6	6
Sequence "320LP160"		6	6	6	6
Sequence "L320160P"		6	6	6	6
Total	25	25	25	25	24

160 = 160 mg Silexan®; 320 = 320 mg Silexan®; P = Placebo; L = Lorazepam

Diagnosis and main criteria for inclusion:

Healthy male and female volunteers aged 25-60 years were included that were active drivers with a driver's licence for at least 3 years and a minimal mileage per year of 3,000 km.

Test preparation, dose, mode of:

Silexan® (WS® 1265): Lavender oil:
Trial part 1: 80 mg Silexan®
Trial part 2: 160 mg and 320 mg Silexan®
Oral administration

Control preparation, dose, mode of:

Placebo:
Trial part 1 & 2: placebo
Oral administration

Placebo Lorazepam:
Trial part 2: placebo
Oral administration

Lorazepam:
Trial part 2: 1.0 mg Lorazepam
Oral administration

Duration of treatment:

Trial part 1:
80 mg Silexan® per day for 8 days
Placebo for 8 days
Wash-out period of between the two crossover periods

Trial part 2:
160 mg and 320 mg Silexan®: each 1 day (single doses)
Placebo: 1 day (single dose)
1.0 mg Lorazepam: 1 day (single dose)
Wash-out period of each 7 days between the four crossover periods

Criteria for evaluation

Primary efficacy variable:

- Standard Deviation of Lane Position (SDLP)

Secondary outcome variables:

- Raters' global assessment of subjects' driving performance on the Fitness-to-Drive-Scale
- Number of driving errors in total and in subcategories

- Subjective assessment of driving performance on the Fitness-to-Drive-Scale
- Eyelid Closure Index in the vigilance section as objective measure of sleepiness.
- Reaction time to sudden events
- Rating on the Stanford Sleepiness Scale

Safety:

- (Serious) adverse events

Statistical methods:

Part 1 and part 2 of the trial were analyzed separately.

Primary efficacy variable:

Trial part 1:

It was hypothesized that the driving performance after an acute intake of 80 mg Silexan® is non-inferior to the driving performance after placebo administration.

Additionally, it was hypothesized that the driving performance after an acute intake of 80 mg Silexan® is equivalent to the driving performance after placebo administration.

The SDLP after acute intake of 80 mg Silexan® and placebo was compared. [redacted]

In the first step, it was investigated if 80 mg single dose Silexan® is non inferior to placebo with respect to driving performance in terms of SDLP. The non-inferiority margin was defined as 2 cm and the equivalence interval of the mean difference between placebo and Silexan® 80 mg was defined as ± 2 cm. Consistently, the null hypothesis of inferiority of 80 mg Silexan® could be rejected with a type I error rate of α=0.05, if the upper limit of the one-sided 95% confidence interval of the contrasts of the two treatments was below the non-inferiority margin of 2 cm. If the corresponding null hypothesis (i.e. 80 mg Silexan® is inferior to placebo with regard to driving performance by SDLP) could be rejected, the null hypothesis stating non-equivalence of Silexan® compared to placebo with respect to driving performance was tested in a second step. Equivalence was tested by interval inclusion (Schwarzer & Schumacher, 2007). This means that the null hypothesis of non-equivalence could be rejected with a type I error rate of α=0.05 if the two-sided 90% confidence interval of the contrasts of the two treatments lay completely in between the limits ± 2 cm. According to the a priori ordered hypotheses this multiple test procedure controls an experiment wise type I

error rate α if the tests are performed at the local level α (Maurer et al. 1995).

Trial part 2:

It was hypothesized that 160 mg Silexan® and 320 mg Silexan® respectively are superior over 1.0 mg Lorazepam with respect to driving fitness.
Furthermore, the comparison of 1.0 mg Lorazepam with placebo served to ensure the internal validity of the experimental set-up.

The SDLP after intake of the different IMPs was compared. [redacted]

In the first step, it was investigated if 160 mg Silexan® is superior to Lorazepam with respect to driving performance in terms of SDLP. The decisions about rejecting or accepting the null-hypotheses were made by application of the multiple testing procedure for ordered hypotheses. Only if the first null-hypothesis (SDLP is equal for 160 mg Silexan® and Lorazepam) could be rejected, the second null-hypothesis (SDLP is equal for 320 mg Silexan® and Lorazepam) could be tested to investigate if 320 mg Silexan® is superior to Lorazepam with respect to driving performance. If the first null-hypothesis was to be accepted, the testing procedure stopped without testing the second null-hypotheses. A local type I error rate α = 0.025 (one-sided) was applied for each test, therefore the multiple test procedure also guaranteed control of the experimentwise type I error rate α (Maurer et al., 1995).

Results of trial part 1:

Baseline demographic data for the full analysis set (FAS) show that the subjects were predominantly Caucasian (97.9%) with slightly more men (54.2%) than women (45.8%). Subjects were on average 33.9 ± 9.0 years old, had a mean height of 177.2 ± 8.5 cm, a mean weight of 84.4 ± 15.1 kg.

Results of Efficacy:

Primary efficacy variable

In the FAS, the mean values of the SDLP were [redacted] after acute intake of Silexan® and placebo. The confirmatory analysis in the FAS by a mixed linear model [redacted] between Silexan® and placebo after acute intake [redacted] with respect to SDLP.

Primary efficacy variable: SDLP after acute intake (FAS)

		Silexan (N=48)	Placebo (N=48)	Difference of LSMEANS "Silexan - Placebo" (Estimate ± Standard Error)	90% CI 95% CI p-value
SDLP [cm]					
Acute intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]

LSMEANS: least square means generated by mixed linear model with random effects for subject within sequence and fixed effects for sequence, period and treatment
SD = Standard deviation, CI = confidence interval

The mean values of the SDLP in the per protocol set (PP) were [redacted] after acute intake of Silexan® and placebo, respectively ([redacted] cm and [redacted] cm, respectively).

Secondary efficacy variables

The analysis of the difference "Silexan - Placebo" of SDLP after acute intake by categories revealed that most frequently subjects were [redacted] ([redacted]) and

the improvements and impairments after acute intake of Silexan® were approximately [redacted] distributed ([redacted]).

The mean values of the SDLP in the FAS were [redacted] after subchronic intake of Silexan® and placebo ([redacted] cm and [redacted] cm, respectively). Thus, the results of the [redacted] by the results of SDLP for subchronic intake.

The analysis of the difference “Silexan - Placebo” of SDLP after subchronic intake by categories revealed that most frequently subjects were [redacted] ([redacted]) and the improvements and impairments after acute intake of Silexan® were approximately [redacted] distributed ([redacted]).

Assessment of driving performance was done separately by raters and subjects on an 11-points-rating scale.

In the FAS, the mean values of the raters’ global assessment of subjects’ driving performance were [redacted] after both, acute intake of Silexan® and placebo and subchronic intake of Silexan® and placebo.

In the FAS, the mean values of the subjective assessment of driving performance were [redacted] after both, acute intake and subchronic intake of Silexan®.

Assessment of driving performance by raters and subjects (FAS)

Parameter		Silexan[1] (N=48)	Placebo (N=48)	Difference of LSMEANS "Silexan - Placebo" (Estimate ± Standard Error)	p-value
Raters' global assessment of subjects' driving performance					
Acute intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Subchronic intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Subjective assessment of driving performance					
Acute intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Subchronic intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]

LSMEANS: least square means generated by mixed linear model with random effects for subject within sequence and fixed effects for sequence, period and treatment; SD = Standard deviation.
[1] N_{miss}=1 after acute intake of Silexan® for raters' global assessment of subjects' driving performance and subjective assessment of driving performance

In the FAS, the mean values of driving errors in total were [redacted] after both, acute intake and subchronic intake of Silexan® and placebo.

Total number of errors and subcategories (FAS)

Parameter		Silexan (N=48)[1]	Placebo (N=48)	Difference of LSMEANS "Silexan - Placebo" (Estimate ±Standard Error)	p-value
Number of driving errors in total					
Acute intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Subchronic intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Tactical errors with respect to longitudinal control					
Acute intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Subchronic intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]

Operational errors with respect to lateral control					
Acute intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Subchronic intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Cognitively based errors					
Acute intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Subchronic intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Number of collisions and critical situations					
Acute intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Subchronic intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]

LSMEANS: least square means generated by mixed linear model with random effects for subject within sequence and fixed effects for sequence, period and treatment
; SD = Standard deviation.
[1] N_{miss}=1 after acute intake of Silexan® for total number of errors and subcategories.

The eyelid closure index was analyzed during the driving test to evaluate sedation and sleepiness.

In the FAS, the mean values of eyelid closure index were [redacted] after the acute intake of Silexan® compared to placebo and [redacted] after subchronic intake of Silexan® and placeboIn the FAS, the mean values of reaction time to sudden events were [redacted] after acute intake and after the subchronic intake of Silexan® and placebo.

Eyelid closure index and reaction time to sudden events (FAS)

Parameter		**Silexan[1] (N=48)**	**Placebo (N=48)**	**Difference of LSMEANS "Silexan - Placebo" (Estimate ± Standard Error)**	**p-value**
Eyelid closure index					
Acute intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Subchronic intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Reaction time to sudden events [s]					
Acute intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]
Subchronic intake	Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]

LSMEANS: least square means generated by mixed linear model with random effects for subject within sequence and fixed effects for sequence, period and treatment
; SD = Standard deviation.
[1] N_{miss}=2 after acute intake of Silexan®, N_{miss}=2 after acute intake of placebo,[1] N_{miss}=3 after subchronic intake of Silexan® and N_{miss}=1 after subchronic intake of placebo for eyelid closure index; N_{miss}=1 after acute intake of Silexan® for reaction time to sudden events.

The subjects evaluated sleepiness subjectively themselves by means of the Stanford Sleepiness Scale

In the FAS, the mean Stanford Sleepiness Scores were [redacted] prior and after acute intake of Silexan® and placebo. Similar results were obtained for subchronic intake.

Stanford Sleepiness Score (FAS)

	Silexan: prior intake (N=48)	**Silexan: after intake (N=48)**	**Placebo: prior intake (N=48)**	**Placebo: after intake (N=48)**	**Difference of LSMEANS "Silexan - Placebo" (Estimate ± Standard Error): with and without covariate baseline**	**p-value**
Acute intake						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subchronic intake						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LSMEANS: least square means generated by mixed linear model with random effects for subject within sequence and fixed effects for sequence, period and treatment
Min = Minimum; Max = Maximum; SD = Standard deviation.
n.a. = not applicable: Calculation with baseline as covariate was not possible due to missing convergence.
Source data: Appendix Part I Tables 16.2.II.5.8.2 and 16.2.II.5.8.3

Similar results were obtained for the PP in all secondary efficacy endpoints.

Results of safety analysis:

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Adverse events

Subsequent analysis reflects the AEs during both the one-week treatment phase and the risk phase (i.e. 2 days starting the day after the last treatment intake). The incidence rate was [redacted] for Silexan® and [redacted] for placebo.

Number and incidence of AEs of any causality (SES, part I)

Treatment	Trial period	Subjects in trial	Subjects (%) with adverse events	Observation days	Number of adverse events	Events per observation days
	Between begin of study and active treatment	50	[redacted]	[redacted]	[redacted]	[redacted]
Silexan®	During active treatment	49	[redacted]	[redacted]	[redacted]	[redacted]
	During risk phase*	49				
	During both active treatment and risk phase*	49	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	During active treatment	49	[redacted]	[redacted]	[redacted]	[redacted]
	During risk phase*	49				
	During both active treatment and risk phase*	49	[redacted]	[redacted]	[redacted]	[redacted]
	After risk phase	50	[redacted]	[redacted]	[redacted]	[redacted]

* Risk phase consists of 2 days after last intake of the investigational product
n.a. = not applicable.

The only notable difference for incidence rates between Silexan® and placebo was the higher incidence of eructation in the Silexan® period. Eructation is a known side effect in patients under oral treatment with Silexan®.

The only notable difference for incidence rates for AEs with suspected causal relationship was the higher incidence of eructation in the Silexan® period. Eructation is a known side effect in patients under oral treatment with Silexan®. The second leading AE with suspected causal relationship was fatigue. In both treatment groups the frequency of fatigue was comparable and in the majority of cases fatigue was reported to be triggered by the 60-minute driving fitness test composed of a representative set of scenarios on highways, rural road and in urban traffic. In particular, the monotonous dark night scenario can facilitate task-related tiredness.

The analysis of the AEs potentially related to the investigational medicinal product yielded similar results as the analysis of the overall AEs. With exception of eructation, no relevant treatment differences with respect to the incidence were observed during the one-week period.

Serious AEs (SAEs) were not reported in part 1 of the clinical trial.

Vital signs

The mean values of systolic and diastolic blood pressure as well as heart rate were similar for Silexan® and placebo for the first and the last day of the intake period.

CONCLUSION OF TRIAL PART 1

Part 1 of this monocentric, randomized, double-blind, placebo-controlled cross-over clinical trial was conducted to test the non-inferiority and equivalence of driving fitness after acute application of 80 mg Silexan® in comparison to placebo in healthy male and female subjects. Both, 80 mg Silexan® and placebo were taken for 8 days, respectively. The first application (single dose) constituted the so-called “acute intake”. Subsequent applications (multiple doses) established the “subchronic” intake. Fitness to drive was measured in a motion-based driving simulator During this so-called “vigilance section” the primary endpoint, the standard deviation of lane position (SDLP) which is an indicator of lane keeping performance, was recorded. Further parameters, like total number of driving errors including subcategories, reaction time to event, eyelid closure index and subjective evaluation of sleepiness by means of the Standord Sleepines Scale were investigated exploratively.

The statistical methods and procedures applied for analysis were specified in detail in the statistical analysis plan before breaking the blind.

For the SDLP, the primary outcome, an adjusted treatment group difference of **xxxxxx** cm [90%-CI: [redacted]] between Silexan® 80 mg and placebo was shown for the acute intake. For the subchronic intake, the mean difference between Silexan® 80 mg and placebo was [redacted] cm [90%-CI: [redacted]]. For the secondary parameters the treatment with Silexan® and placebo showed [redacted] results. For the number of errors in total and in each subcategory during the driving test after both, acute and subchronic intake, the mean differences between both treatments were [redacted]. Also further investigations (eyelid closure index, reaction time to sudden events) and assessments (raters’ and subjects’ global assessment of driving performance, rating on the Stanford Sleepiness Scale) [redacted] with the results described above.

The overall incidence rate of AEs was elevated in the Silexan® period compared to placebo during the one-week intake and subsequent two-day risk phase. With exception of eructation which is a known ADR of Silexan® no relevant treatment differences with respect to the incidence of ADRs were observed.. No SAEs were reported in part 1 of the trial. Furthermore, no safety signals could be detected from vital signs. In summary, the first part

of the trial [redacted] of Silexan® compared to placebo with regard to driving fitness. Silexan® was well tolerated and no new safety concern has been detected in this trial.

Results of trial part 2:

Baseline demographic data for the full analysis set (FAS) show that all subjects were Caucasians (100.0%) with slightly more women (56.0%) than men (44.0%). Subjects were on average 33.1 ± 9.8 years old, had a mean height of 171.3 ± 8.3 cm, a mean weight of 79.6 ± 16.2 kg.

Results of Efficacy:

Primary efficacy variable

The mean values of the SDLP were [redacted] after the intake of 160 mg Silexan®, 320 mg Silexan® and placebo but clearly [redacted] than after the intake of 1.0 mg Lorazepam.

Primary efficacy variable: SDLP (FAS)

	160 mg Silexan (N=25)	320 mg Silexan (N=25)[1]	1.0 mg Lorazepam (N=25)	Placebo (N=25)	Difference of LSMEANS "160 mg / 320 mg Silexan - 1.0 mg Lorazepam" (Estimate ± Standard Error)	p-value "160 mg / 320 mg Silexan - 1.0 mg Lorazepam"
SDLP [cm]						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LSMEANS: least square means generated by mixed linear model with random effects for subject within sequence and fixed effects for sequence, period and treatment
; SD = Standard deviation.
[1] N_{miss}=1 for SDLP.

The mean values of the SDLP in the per protocol set (PP) were [redacted] after intake of 160 mg Silexan®, 320 mg Silexan® and placebo ([redacted] cm, [redacted] cm and [redacted] cm, respectively) but clearly [redacted] than after intake of 1.0 mg Lorazepam ([redacted] cm).

Secondary efficacy variables

The analysis of the difference "Silexan - Lorazepam" of SDLP by categories revealed that an [redacted] was obtained for the broad majority of subjects (160 mg Silexan®: [redacted], [redacted] 320 mg Silexan®: [redacted]). The remaining subjects had differences of ± 2 cm except [redacted].

Assessment of driving performance was done separately by raters and subjects on an 11-points-rating scale

In the FAS, the mean values of the raters' global assessment of subjects' driving performance were [redacted] after the intake of 160 mg Silexan®, 320 mg Silexan® and placebo [redacted] than after the intake of 1.0 mg Lorazepam. In the FAS, the mean values of the subjective assessment of driving performance were [redacted] after the intake of 320 mg Silexan® and placebo but [redacted] after the intake of 160 mg Silexan® which was [redacted] than after intake of 1.0 mg Lorazepam.

Assessment of driving performance by raters and subjects (FAS)

	160 mg Silexan (N=25)	320 mg Silexan (N=25)[1]	1.0 mg Lorazepam (N=25)	Placebo (N=25)	Difference of LSMEANS "160 mg / 320 mg Silexan - 1.0 mg Lorazepam" (Estimate ± Standard Error)	p-value "160 mg / 320 mg Silexan - 1.0 mg Lorazepam"
Raters' global assessment of subjects' driving performance						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subjective assessment of driving performance						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LSMEANS: least square means generated by mixed linear model with random effects for subject within sequence and fixed effects for sequence, period and treatment
; SD = Standard deviation.
[1] N_{miss}=1 for raters' global assessment of subjects' driving performance.

In the FAS, the mean values of driving errors in total were [redacted] after the intake of 160 mg Silexan®, 320 mg Silexan® and placebo [redacted] than after the intake of 1.0 mg Lorazepam

Total number of errors and subcategories (FAS)

	160 mg Silexan (N=25)	320 mg Silexan (N=25)[1]	1.0 mg Lorazepam (N=25)	Placebo (N=25)	Difference of LSMEANS "160 mg / 320 mg Silexan - 1.0 mg Lorazepam" (Estimate ± Standard Error)	p-value "160 mg / 320 mg Silexan - 1.0 mg Lorazepam"
Number of driving errors in total						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tactical errors with respect to longitudinal control						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Operational errors with respect to lateral control						

Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cognitively based errors						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of collisions and critical situations						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LSMEANS: least square means generated by mixed linear model with random effects for subject within sequence and fixed effects for sequence, period and treatment
; SD = Standard deviation.
[1] N_{miss}=1 for total number of errors and subcategories.

The eyelid closure index was analyzed during the driving test to evaluate sedation and sleepiness.

In the FAS, the mean values of the eyelid closure index were [redacted] after intake of 160 mg Silexan® compared to the other treatments.

Eyelid closure index (FAS)

	160 mg Silexan (N=25)	**320 mg Silexan (N=25)[1]**	**1.0 mg Lorazepam (N=25)[1]**	**Placebo (N=25)[1]**	**Difference of LSMEANS "160 mg / 320 mg Silexan - 1.0 mg Lorazepam" (Estimate ± Standard Error)**	**p-value "160 mg / 320 mg Silexan - 1.0 mg Lorazepam"**
Eyelid closure index						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LSMEANS: least square means generated by mixed linear model with random effects for subject within sequence and fixed effects for sequence, period and treatment
; SD = Standard deviation.
[1] N_{miss}=1 after intake of 320 mg Silexan®, N_{miss} = 1 after intake of 1.0 mg Lorazepam and N_{miss} = 1 after intake of placebo for eyelid closure index.

In the FAS, the mean (median) values of reaction time to sudden events were [redacted] after the intake of 160 mg Silexan®, 320 mg Silexan® and placebo [redacted] compared to Lorazepam.

Reaction time to sudden events (FAS)

	160 mg Silexan (N=25)	320 mg Silexan (N=25)[1]	1.0 mg Lorazepam (N=25)	Placebo (N=25)	Difference "160 mg / 320 mg Silexan - 1.0 mg Lorazepam" (Mean ± Standard Deviation)	p-value "160 mg / 320 mg Silexan - 1.0 mg Lorazepam"
Reaction time to sudden events [s]						
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

; SD = Standard deviation.
[1] N_{miss}=1 for reaction time to sudden events.

The subjects evaluated sleepiness subjectively themselves by means of the Stanford Sleepiness Scale

In the FAS, the mean Stanford Sleepiness Scores were [redacted] prior and after the intake of 160 mg Silexan®, 320 mg Silexan®, 1.0 mg Lorazepam and placebo.

Stanford Sleepiness Score (FAS)

	160 mg Silexan: prior intake (N=25)	160 mg Silexan: post intake (N=25)	320 mg Silexan: prior intake (N=25)	320 mg Silexan: post intake (N=25)	1.0 mg Lora-zepam: prior intake (N=25)	1.0 mg Lora-zepam: post intake (N=25)	Placebo: prior intake (N=25)	Placebo: post intake (N=25)
Mean ± SD	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Mean Difference "160 mg / 320 mg Silexan - 1.0 mg Lorazepam" (Estimate ± Standard Error): without covariate baseline	p-value "160 mg / 320 mg Silexan - 1.0 mg Lorazepam
[redacted]	[redacted]

; SD = Standard deviation.
Note: Calculation with baseline as covariate was not possible due to missing convergence.

Similar results were obtained for the PP in all secondary efficacy endpoints.

Results of safety analysis:

Adverse events

The incidence rate was [redacted] for Lorazepam, [redacted] for Silexan® 160 mg and [redacted] for Silexan® 320 mg. For placebothe incidence rate was [redacted].

Number and incidence of AEs of any causality (SES, part II)

Treatment	Trial period	Subjects in trial	Subjects (%) with adverse events	Observation days	Number of adverse events	Events per observation days
	Between begin of study and active treatment	25	[redacted]	[redacted]	[redacted]	[redacted]
160 mg Silexan®	During active treatment	25	[redacted]	[redacted]	[redacted]	[redacted]
	During risk phase*	25	[redacted]	[redacted]	[redacted]	[redacted]
	During both active treatment and risk phase*	25	[redacted]	[redacted]	[redacted]	[redacted]
320 mg Silexan®	During active treatment	25	[redacted]	[redacted]	[redacted]	[redacted]
	During risk phase*	25	[redacted]	[redacted]	[redacted]	[redacted]
	During both active treatment and risk phase*	25	[redacted]	[redacted]	[redacted]	[redacted]
1.0 mg Lorazepam	During active treatment	25	[redacted]	[redacted]	[redacted]	[redacted]
	During risk phase*	25	[redacted]	[redacted]	[redacted]	[redacted]
	During both active treatment and risk phase*	25	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	During active treatment	25	[redacted]	[redacted]	[redacted]	[redacted]
	During risk phase*	25	[redacted]	[redacted]	[redacted]	[redacted]
	During both active treatment and risk phase*	25	[redacted]	[redacted]	[redacted]	[redacted]
	After risk phase	25	[redacted]	[redacted]	[redacted]	[redacted]

* Risk phase consists of 2 days after last intake of the investigational product
n.a. = not applicable.

The incidence rate of AE potentially related was [redacted] in the Lorazepam period, [redacted] in the 160 mg Silexan® period and [redacted] in the 320 mg Silexan® period. In the placebo period, the incidence rate was [redacted].

Fatigue and dizziness were reported more frequently after intake of 1.0 mg Lorazepam compared to Silexan®. Furthermore, the intensity of fatigue was more often severe for Lorazepam compared to Silexan®. The frequency of fatigue and dizziness after the intake of Silexan® was comparable to placebo.The only notable difference for incidence rates between Silexan® 160 and 320 mg compared to placebo was the higher incidence of eructation in the Silexan® period. Eructation is a known ADR of Silexan®, fatigue and dizziness are known ADRs of lorazepam.

The analysis of the AEs potentially related to the investigational product yielded similar results as the analysis of the overall AEs.

Serious AEs (SAEs) were not reported in this clinical trial.

Vital signs

The mean values of systolic and diastolic blood pressure as well as heart rate were similar for 160 mg Silexan®, 320 mg Silexan®, 1.0 mg Lorazepam and placebo - each prior and after intake, respectively.

CONCLUSION OF TRIAL PART 2

Part 2 of this monocentric, randomized, double-blind, placebo- and reference-controlled cross-over clinical trial was conducted to test in 2 steps the superiority first of 160 mg Silexan® (“160”) and - if successful - subsequently of 320 mg Silexan® (“320”) in comparison to 1.0 mg Lorazepam (“L”) regarding the driving fitness in healthy male and female subjects. In addition, placebo (“P”) was given to demonstrate assay sensitivity. Fitness to drive was measured the same way as in part 1.

The statistical methods and procedures applied for analysis were specified in detail in the statistical analysis plan for part 2 of the clinical trial before breaking the blind.

For the SDLP, the primary outcome, a [redacted] treatment group difference for both Silexan® 160 mg ([redacted] cm [95%-CI: [redacted]]) and Silexan® 320 mg ([redacted] cm [95%-CI: [redacted]]) compared to Lorazepam could be shown. The [redacted] by the results in the secondary outcomes for both Silexan® doses. Furthermore, the study validity was [redacted] treatment difference for placebo compared to Lorazepam and the [redacted] results in the secondary outcomes for placebo, which were [redacted].

The only notable difference for incidence rates between Silexan® 160 and 320 mg compared to placebo was the higher incidence of eructation in the Silexan® period. Eructation is a known ADR of Silexan®, fatigue and dizziness are known ADRs of Lorazepam.

Measurement of vital signs in part 2 of the clinical did not reveal clinically relevant differences neither between 160 mg Silexan®, 320 mg Silexan®, 1.0 mg Lorazepam and placebo nor prior and after intake, respectively.

In summary, the second part of the trial [redacted] of Silexan® compared to Lorazepam with regard to driving fitness. Furthermore, the superiority of placebo compared

to Lorazepam demonstrated the validity of the trial design and the sensitivity of the measures for detecting effects of driving fitness. Silexan® was well tolerated and no new safety concern has been detected in this trial.

OVERALL CONCLUSION OF TRIAL PART 1 AND 2

In part 1 of this cross over double-blind clinical trial the [redacted] of the intake of 80 mg Silexan® compared to placebo was [redacted] regarding the driving fitness investigated by means of SDLP during driving tests in a motion-based simulator consisting of a representative set of scenarios on highways, rural road and in urban traffic. In part 2 [redacted] of 160 mg and 320 mg Silexan® versus 1.0 mg Lorazepam [redacted] after a single dose intake applying the same tests. Only a few of these investigations [redacted] but in almost all cases the outcome (Silexan® 160/320 mg versus 1.0 mg Lorazepam) [redacted] with the differences between placebo and 1.0 mg Lorazepam. Thus, Silexan® [redacted] the driving fitness of healthy subjects compared to placebo under these trial conditions. Silexan® was well tolerated and no new safety concern has been detected in this trial. All in all, the clinical trial demonstrated the non-sedating potential of Silexan®.

References

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