Summary of results
Version 1.0

Proof of concept trial to evaluate the effectiveness of combined treatment with Valerian extract and Lavender oil in patients suffering from inability to fall or stay asleep

Clinical trial no. 750598.01.003

EudraCT no. 2015-003265-29

Date of report: 20 December 2019

First patient enrolled: 30 August 2016

Last patient completed: 12 May 2018

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1 SUMMARY

Sponsor:	Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany
Title of clinical trial:	Proof of concept trial to evaluate the effectiveness of combined treatment with Valerian extract and Lavender oil in patients suffering from inability to fall or stay asleep
Relevant amendments:	**Protocol Amendment No. 01** The determination of the creatinine clearance was replaced by the determination of the glomerular filtration rate. The allowed time for the Digit-symbol substitution test (DSST) has been prolonged from 90 to 120 seconds. 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. **Protocol Amendment No. 02** 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. The inclusion criteria Wake-time during sleep, Total sleep time (TST) and Insomnia Severity Index (ISI) were adapted. **Protocol Amendment No. 03 and No. 04** The exclusion criterion regarding concomitant diseases was changed.
Coordinating investigator	One co-ordinating investigator in Germany
Investigators:	The study was conducted by one investigator in Germany
Trial sites:	The study was conducted by one investigator in Germany
Trial period:	First patient enrolled: 30 August 2016 Last patient completed: 12 May 2018
Publications:	None
Clinical phase:	Phase II

Objective: The objective of this exploratory trial was to assess the effectiveness of a combined treatment (Synalan) with Valerian extract and Silexan (Lavender oil) in patients with inability to fall or stay asleep.

Methodology: This randomized, double-blind, reference-controlled phase II clinical trial was conducted in a cross-over design with three periods, three treatments (combined treatment [Valerian extract + Silexan (Lavender oil)] and two reference treatments [Valerian extract + Lavender oil placebo] and [Lavender oil + Valerian placebo]) and six sequences.
Final assessments were done after three days of treatment at the respective visits of the periods. The periods were separated by a wash-out period of 7 days.

Number of patients included in the analysis: 108 female patients, 65 male patients and 2 patients with missing information about gender, i.e. in total 175 patients, were screened. Two of these patients were re-screened due to scheduling conflicts (PSG bed limitation). 19 eligible female and 13 male patients, i.e. in total 32, were randomized. 30 patients completed the trial according to the protocol.

Planned to be randomized to sequence groups	Patients taken into account for the analysis of				
			Safety	Effectiveness	
	Included	Randomized	Safety set	Full analysis set	Per protocol set
Silexan - Synalan - Valeriana:	5	5	5	5	5
Silexan - Valeriana - Synalan:	5	5	5	5	5
Synalan - Silexan - Valeriana:	5	5	5	5	5
Synalan - Valeriana - Silexan:	6	6	6	5	5
Valeriana - Silexan - Synalan:	5	5	5	5	5
Valeriana - Synalan - Silexan:	6	6	6	6	5
Total	32	32	32	31	30

Source: Appendix 16.2.II, Table 2.2

Diagnosis and main criteria for inclusion:

Nonorganic insomnia (ICD 10 F51.0) is a condition of unsatisfactory quantity and/or quality of sleep, which persists for a considerable period of time, including difficulty falling asleep, difficulty staying asleep, or early final wakening.

Main criteria for inclusion:
1. Patients not able to fall or stay asleep with a diagnosis of non-organic insomnia:

a) According to ICD 10 F 51.0

- A complaint of difficulty falling asleep, maintaining sleep, or non-refreshing sleep.
- The sleep disturbance occurs at least three times per week for at least one month.
- The sleep disturbance results in marked personal distress or interference with personal functioning in daily living.
- Absence of any known causative organic factor, such as a neurological or other medical condition, psychoactive substance use disorder or a medication.

b) According to PSG screening criteria:

- 2-night mean latency to persisting sleep (LPS) > 30 min
- Wake-time during sleep (WTDS) > 30 min
- Total sleep time (TST) > 180 min and < 390 min

2. No organic reason for sleep disturbances.
3. Insomnia Severity Index (ISI) score ≥ 15 at screening.
4. Patients otherwise healthy / medically stable on the basis of clinical laboratory tests, medical history, vital signs, and 12-lead electrocardiography (ECG) performed at screening. The patient was included only if the investigator judged the abnormalities or deviations from normal to be not clinically significant or to be appropriate and reasonable for the population under trial. His / her decision was to be recorded in the patient's source documents and initialed by the investigator.
5. Patients aged between 18 and 50 years (at the time of informed consent).

Investigational product, dose and mode of administration:

A combination of Valerian extract and Lavender oil/Silexan®.
Dosage: [redacted]/die Valerian extract in form of film coated tablets and [redacted]/die Lavender oil/Silexan® in form of soft gel capsules .
The investigational medicinal product (IMP) was administered with a glass of water and was swallowed as a whole and was not

chewed, divided, dissolved or crushed.

Control preparation, dose and mode of administration,:

Reference 1:
Valerian extract in form of film coated tablets and Placebo in form of soft gelatin capsules containing no active drug.
Reference 2:
Lavender oil in form of soft gel capsules and Placebo in form of film coated tablets containing no active drug.

Duration of treatment:

Within each of the three treatment periods the trial medication was taken over the course of three consecutive days.

Criteria for evaluation

Effectiveness:

Effectiveness was assessed by the following endpoints:

- Polysomnographic endpoints
  - Wake time during sleep (WTDS)
  - Sleep onset latency (SOL)
  - Wake time after sleep onset (WASO)
  - Number of awakenings after sleep onset (NAASO)
  - Total sleep time (TST)
  - Latency to persistent sleep (LPS)
  - Sleep efficiency during time in bed (SE TIB)
  - Sleep efficiency during sleeping time (SE SPT)
  - Wake time after sleep (WTAS)
- Subjective endpoints (self-rating, subjective sleep measures)
  - Subjective sleep onset latency (sSOL)
  - Subjective wake time after sleep onset (sWASO)
  - Subjective number of awakenings after sleep onset (sNAASO)
  - Subjective total sleep time (sTST)
  - Quality of sleep (last night)
  - Leeds sleep evaluation questionnaire (LSEQ) (GTS-, QOS-, AFS- and BFW-sub-score)
- Endpoints of subsequent daytime functioning
  - Modified Karolinska sleepiness scale (mKSS)
  - Digit-symbol-substitution test (DSST)

Safety:

Safety was assessed according to the following endpoints:

- Occurrence of serious (SAEs) and non-serious adverse events (AEs)

- Vital signs
- Physical examination findings
- ECG

Statistical methods: All effectiveness analyses were based on the same approach: All endpoints were compared between Synalan and both reference treatments (i.e. Synalan vs. Valeriana and Synalan vs. Silexan)
Due to the explorative nature of this trial these endpoints were not classified as primary or secondary, and no adjustment for multiplicity was performed.
Missing data were not imputed or replaced, and analyses were based only on non-missing data.

RESULTS

Demographic data:

Demographic data (FAS)

Demographic data (FAS)		Sequence groups													
		Sil - Syn - Val (N=5)		Sil - Val - Syn (N=5)		Syn - Sil - Val (N=5)		Syn - Val - Sil (N=5)		Val - Sil - Syn (N=5)		Val - Syn - Sil (N=6)		Total (N=31)	
		n	%	n	%	n	%	n	%	n	%	n	%	n	%
Sex															
Male		2	40.0	3	60.0	2	40.0	1	20.0	3	60.0	2	33.3	13	41.9
Female		3	60.0	2	40.0	3	60.0	4	80.0	2	40.0	4	66.7	18	58.1
Age [years]	Mean (±SD)	31.4 (±8.73)		36.4 (±8.85)		30.2 (±3.96)		35.6 (±10.06)		37.6 (±8.26)		37.2 (±6.40)		34.8 (±7.78)	
	Min. - Max.	23 - 46		26 - 49		27 - 35		25 - 47		27 - 47		30 - 48		23 - 49	
Weight [kg]	Mean (±SD)	71.4 (±5.03)		67.0 (±11.11)		73.4 (±13.87)		68.4 (±9.45)		71.0 (±10.75)		67.3 (±9.85)		69.7 (±9.73)	
	Min. - Max.	66 - 77		55 - 79		59 - 88		57 - 82		62 - 87		57 - 83		55 - 88	

Source: Appendix 16.2.II, Table 4.1

Results of effectiveness:

Summary of polysomnographic endpoints (PSG) during treatment phase at Day 3 of Sleep Laboratory nights (FAS)

Polysomnographic endpoints (PSG) during treatment phase at Day 3 of Sleep Laboratory nights (FAS)		Treatment periods			
		Screening (N=31)	Synalan (N=31)	Valeriana (N=31)	Silexan (N=31)
	valid N | N missing	31 | 0	31 | 0	31 | 0	30 | 1
Wake time during sleep [min] (WTDS)	Mean (±SD)	85.97 (±40.799)			
	geom. Mean (CV%)	76.82 (47.5%)			
	Median (Q25% - Q75%)	73.00 (58.00 - 114.50)			
	Min. - Max.	31.0 - 180.0			
Sleep onset latency [min] (SOL)	Mean (±SD)	42.42 (±29.984)			
	geom. Mean (CV%)	31.01 (70.7%)			
	Median (Q25% - Q75%)	38.70 (19.30 - 61.30)			
	Min. - Max.	4.0 - 111.5			
Wake time after sleep onset [min] (WASO)	Mean (±SD)	96.06 (±43.132)			
	geom. Mean (CV%)	86.93 (44.9%)			
	Median (Q25% - Q75%)	84.60 (64.50 - 120.00)			
	Min. - Max.	31.1 - 212.0			
Number of awakenings after sleep onset (NAASO)	Mean (±SD)	35.5 (±13.92)			
	geom. Mean (CV%)	33.3 (39.2%)			
	Median (Q25% - Q75%)	32.0 (24.0 - 48.0)			
	Min. - Max.	18 - 83			
Total sleep time (TST) [min]	Mean (±SD)	340.83 (±48.432)			
	geom. Mean (CV%)	336.88 (14.2%)			
	Median (Q25% - Q75%)	352.00 (317.00 - 378.50)			
	Min. - Max.	186.5 - 398.5			
Latency to persistent sleep [min] (LPS)	Mean (±SD)	65.60 (±38.463)			
	geom. Mean (CV%)	53.85 (58.6%)			
	Median (Q25% - Q75%)	55.50 (31.00 - 97.00)			
	Min. - Max.	9.0 - 144.0			
Sleep efficiency [%] (SE-TIB)	Mean (±SD)	71.12 (±10.193)			
	geom. Mean (CV%)	70.28 (14.3%)			
	Median (Q25% - Q75%)	73.30 (66.00 - 79.10)			
	Min. - Max.	38.8 - 83.0			
Sleep efficiency [%] (SE-SPT)	Mean (±SD)	79.84 (±9.911)			
	geom. Mean (CV%)	79.17 (12.4%)			
	Median (Q25% - Q75%)	82.00 (74.70 - 87.00)			
	Min. - Max.	50.9 - 92.6			
Wake time after sleep [min] (WTAS)	Mean (±SD)	10.10 (±15.470)			
	geom. Mean (CV%)	0.00 (153.2%)			
	Median (Q25% - Q75%)	0.70 (0.00 - 22.50)			
	Min. - Max.	0.0 - 50.8			

Source: Appendix 16.2.II, Tables 6.2.1.1 to 6.2.1.9

Summary of subjective endpoints during treatment phase at Day 3 of Sleep Laboratory nights (FAS)

Subjective endpoints during treatment phase at Day 3 of Sleep Laboratory nights (FAS)		Treatment periods			
		Screening (N=31)	Synalan (N=31)	Valeriana (N=31)	Silexan (N=31)
	valid N | $N_{missing}$	31 | 0	31 | 0	31 | 0	30 | 1
How long did it take until you fell asleep for the first time? [Minutes] (sSOL)	Mean (±SD)	73.4 (±35.81)			
	geom. Mean (CV%)	65.1 (48.8%)			
	Median (Q25% - Q75%)	60.0 (45.0 - 90.0)			
	Min. - Max.	25 - 180			
How long were you awake after sleep onset until you got up? [Minutes] (sWASO)	Mean (±SD)	104.4 (±72.14)			
	geom. Mean (CV%)	77.4 (69.1%)			
	Median (Q25% - Q75%)	90.0 (40.0 - 150.0)			
	Min. - Max.	10 - 270			
How often did you wake at night? (sNAASO)	Mean (±SD)	4.6 (±2.46)			
	geom. Mean (CV%)	4.1 (53.3%)			
	Median (Q25% - Q75%)	4.0 (3.0 - 5.0)			
	Min. - Max.	2 - 12			
How long have you been sleeping in total? [Minutes] (sTST)	Mean (±SD)	295.2 (±57.89)			
	geom. Mean (CV%)	289.4 (19.6%)			
	Median (Q25% - Q75%)	300.0 (240.0 - 360.0)			
	Min. - Max.	180 - 390			
Quality of sleep (last night)[>] [11-point-rating scale]	Mean (±SD)	3.5 (±1.52)			
	geom. Mean (CV%)	0.0 (43.4%)			
	Median (Q25% - Q75%)	4.0 (3.0 - 5.0)			
	Min. - Max.	0 - 7			

[>] higher is better

Source: Appendix 16.2.II, Tables 6.2.2.1.1 to 6.2.2.1.5

Summary of LSEQ-scores during treatment phase at Day 3 of Sleep Laboratory nights (FAS)

LSEQ-scores during treatment phase at Day 3 of Sleep Laboratory nights (FAS)		Treatment periods		
		Synalan (N=31)	Valeriana (N=31)	Silexan (N=31)
	valid N | N missing	31 | 0	31 | 0	30 | 1
LSEQ-GTS-Score (Getting To Sleep) <	Mean (±SD)	[redacted]	[redacted]	[redacted]
	geom. Mean (CV%)	[redacted]	[redacted]	[redacted]
	Median (Q25% - Q75%)	[redacted]	[redacted]	[redacted]
	Min. - Max.	[redacted]	[redacted]	[redacted]
LSEQ-QOS-Score (Quality Of Sleep) <	Mean (±SD)	[redacted]	[redacted]	[redacted]
	geom. Mean (CV%)	[redacted]	[redacted]	[redacted]
	Median (Q25% - Q75%)	[redacted]	[redacted]	[redacted]
	Min. - Max.	[redacted]	[redacted]	[redacted]
LSEQ-AFS-Score (Awake Following Sleep) <	Mean (±SD)	[redacted]	[redacted]	[redacted]
	geom. Mean (CV%)	[redacted]	[redacted]	[redacted]
	Median (Q25% - Q75%)	[redacted]	[redacted]	[redacted]
	Min. - Max.	[redacted]	[redacted]	[redacted]
LSEQ-BFW-Score (Behaviour Following Wakening) <	Mean (±SD)	[redacted]	[redacted]	[redacted]
	geom. Mean (CV%)	[redacted]	[redacted]	[redacted]
	Median (Q25% - Q75%)	[redacted]	[redacted]	[redacted]
	Min. - Max.	[redacted]	[redacted]	[redacted]

< lower is better

Source: Appendix 16.2.II, Tables 6.2.2.2.1 to 6.2.2.2.4

Summary of subjective endpoints during treatment phase at Day 1 of Sleep Laboratory nights (FAS)

Subjective endpoints during treatment phase at Day 1 of Sleep Laboratory nights (FAS)		Treatment periods			
		Screening (N=31)	Synalan (N=31)	Valeriana (N=31)	Silexan (N=31)
How long did it take until you fell asleep for the first time? [Minutes] (sSOL)	Mean (±SD)	*73.4 (±35.81)*			
	geom. Mean (CV%)	*65.1 (48.8%)*			
	Median (Q25% - Q75%)	*60.0 (45.0 - 90.0)*			
	Min. - Max.	*25 - 180*			
	valid N | N missing	*31 | 0*			
How long were you awake after sleep onset until you got up? [Minutes] (sWASO)	Mean (±SD)	*104.4 (±72.14)*			
	geom. Mean (CV%)	*77.4 (69.1%)*			
	Median (Q25% - Q75%)	*90.0 (40.0 - 150.0)*			
	Min. - Max.	*10 - 270*			
	valid N | N missing	*31 | 0*			
How often did you wake at night? (sNAASO)	Mean (±SD)	*4.6 (±2.46)*			
	geom. Mean (CV%)	*4.1 (53.3%)*			
	Median (Q25% - Q75%)	*4.0 (3.0 - 5.0)*			
	Min. - Max.	*2 - 12*			
	valid N | N missing	*31 | 0*			
How long have you been sleeping in total? [Minutes] (sTST)	Mean (±SD)	*295.2 (±57.89)*			
	geom. Mean (CV%)	*289.4 (19.6%)*			
	Median (Q25% - Q75%)	*300.0 (240.0 - 360.0)*			
	Min. - Max.	*180 - 390*			
	valid N | N missing	*31 | 0*			
Quality of sleep (last night) [>] [11-point-rating scale]	Mean (±SD)	*3.5 (±1.52)*			
	geom. Mean (CV%)	*0.0 (43.4%)*			
	Median (Q25% - Q75%)	*4.0 (3.0 - 5.0)*			
	Min. - Max.	*0 - 7*			
	valid N | N missing	*31 | 0*			

[>] higher is better

Source: Appendix 16.2.II, Tables 6.2.3.1 to 6.2.3.5

Summary of subsequent daytime functioning during treatment phase (FAS)

Subsequent daytime functioning during treatment phase (FAS)		Treatment periods			
		Screening (N=31)	Synalan (N=31)	Valeriana (N=31)	Silexan (N=31)
Day 3 of Sleep Laboratory nights					
Subjective sleepiness scale (MKSS) [<]	Mean (±SD)	6.6 (±1.43)	[redacted]	[redacted]	[redacted]
	geom. Mean (CV%)	6.4 (21.8%)	[redacted]	[redacted]	[redacted]
	Median (Q25% - Q75%)	7.0 (6.0 - 8.0)	[redacted]	[redacted]	[redacted]
	Min. - Max.	3 - 9	[redacted]	[redacted]	[redacted]
	valid N | N missing	31 | 0	[redacted]	[redacted]	[redacted]
Score of Digit-Symbol-Substitution Test (DSST) [>]	Mean (±SD)	75.5 (±14.89)	[redacted]	[redacted]	[redacted]
	geom. Mean (CV%)	74.0 (19.7%)	[redacted]	[redacted]	[redacted]
	Median (Q25% - Q75%)	75.0 (64.0 - 86.0)	[redacted]	[redacted]	[redacted]
	Min. - Max.	52 - 108	[redacted]	[redacted]	[redacted]
	valid N | N missing	31 | 0	[redacted]	[redacted]	[redacted]
Day 1 of Sleep Laboratory nights					
Subjective sleepiness scale [<]	Mean (±SD)		[redacted]	[redacted]	[redacted]
	geom. Mean (CV%)		[redacted]	[redacted]	[redacted]
	Median (Q25% - Q75%)		[redacted]	[redacted]	[redacted]
	Min. - Max.		[redacted]	[redacted]	[redacted]
	valid N | N missing		[redacted]	[redacted]	[redacted]

[<] lower is better

[>] higher is better

Source: Appendix 16.2.II, Tables 6.2.4.1, 6.2.4.2 and 6.2.5.1

All three treatments [redacted] compared to the screening values (without treatment). Synalan showed [redacted] of the polysomnographic and subjective endpoints compared to Valeriana. The [redacted] for Synalan vs. Valeriana were shown for [redacted] in the polysomnographic endpoints and for the [redacted] in the subjective endpoints. For the comparison of the endpoints between Synalan and Silexan treatment [redacted] regarding all endpoints.

Results of safety analysis

Adverse events

Number and incidence of adverse events (SAF)

Adverse Events Trial phase (SAF)	Synalan (N=32)				Valeriana (N=31)				Silexan (N=31)				Total (N=32)			
	N events	Mean number of Observed days	Mean number of events per day	Patients with ≥1 AE	N events	Mean number of Observed days	Mean number of events per day	Patients with ≥1 AE	N events	Mean number of Observed days	Mean number of events per day	Patients with ≥1 AE	N events	Mean number of Observed days	Mean number of events per day	Patients with ≥1 AE
Between begin of trial and begin of 1st trial period*													8	586	0.0137	8 (25.0%)
Active treatment phase	3	96	0.0313	3 (9.4%)	0	93	0.0000	0 (0.0%)	0	91	0.0000	0 (0.0%)	3	280	0.0107	3 (9.4%)
Risk phase	2	96	0.0208	2 (6.3%)	1	93	0.0108	1 (3.2%)	1	93	0.0108	1 (3.2%)	4	282	0.0142	3 (9.4%)
Active treatment phase and Risk phase	5	192	0.0260	5 (15.6%)	1	186	0.0054	1 (3.2%)	1	184	0.0054	1 (3.2%)	7	562	0.0125	6 (18.8%)
After risk phase*													2	310	0.0065	2 (6.3%)

* presentation only as total sum as AEs from between begin of the trial and begin of 1st trial period phase and after-risk phase are not allocated to treatment periods according to the SAP (for details see SAP chapter 7.3.3.1 Adverse events)

Source: Appendix 16.2.II, Table 7.1

Serious adverse events (safety analysis set)

No serious adverse events were observed during this trial.

Vital Signs

Summary of vital signs during treatment periods (SAF)

Vital signs during treatment periods (SAF)		Treatment periods		
		Synalan (N=32)	Valeriana (N=31)	Silexan (N=31)
	valid N | N $_{missing}$	31 | 1	31 | 0	30 | 1
Systolic Blood Pressure [mmHg]	Mean (±SD)	121.8 (±13.93)	120.9 (±13.33)	119.6 (±13.21)
	Median (Q25% - Q75%)	119.0 (116.0 - 129.0)	125.0 (112.0 - 130.0)	119.5 (110.0 - 126.0)
	Min. - Max.	82 - 151	83 - 148	94 - 151
Diastolic Blood Pressure [mmHg]	Mean (±SD)	71.1 (±7.67)	72.1 (±8.46)	71.1 (±7.22)
	Median (Q25% - Q75%)	69.0 (65.0 - 76.0)	74.0 (64.0 - 78.0)	70.0 (67.0 - 74.0)
	Min. - Max.	57 - 91	57 - 88	57 - 87
Heart Rate [1/min]	Mean (±SD)	73.0 (±11.10)	72.5 (±10.25)	71.7 (±10.09)
	Median (Q25% - Q75%)	73.0 (64.0 - 81.0)	72.0 (65.0 - 75.0)	73.5 (67.0 - 77.0)
	Min. - Max.	51 - 95	55 - 103	51 - 94
Body Temperature [°C]	Mean (±SD)	36.45 (±0.389)	36.52 (±0.304)	36.41 (±0.417)
	Median (Q25% - Q75%)	36.40 (36.10 - 36.80)	36.50 (36.30 - 36.70)	36.35 (36.10 - 36.70)
	Min. - Max.	35.5 - 37.2	35.7 - 37.3	35.7 - 37.2

Source: Appendix 16.2.II, Tables 9.1.1 to 9.1.4

Physical examination

The physical examination revealed no relevant findings at screening and no relevant findings at the end of trial.

ECG

Shift-table of ECG evaluation by investigator at Screening and End of Trial (SAF)

		Visit 1 (Screening)			
		normal	abnormal, clinically not relevant	abnormal, clinically relevant	**Total**
Visit 10 (End of Trial)					
normal	n (%)[a]	9 (75.0%)	5 (25.0%)	0 (0.0%)	14 (43.75%)
abnormal, clinically not relevant	n (%)[a]	3 (25.0%)	15 (75.0%)	0 (0.0%)	18 (56.25%)
abnormal, clinically relevant	n (%)[a]	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	**n (%)[a]**	**12 (37.5%)**	**20 (62.5%)**	**0 (0.0%)**	**32 (100.0%)**

Explanation:
[a)] Relative frequencies (percent values) of stages at end of therapy are column percents, i.e. the total number of one stage at screening visit is the denominator of the percent value.

Source: Appendix 16.2.II, Table 9.8

The overall incidence of AEs and the rate of AEs per observation days was low during all active treatments and the subsequent respective 3-day risk phase. There was no accumulation of AEs with regard to SOCs and PTs. The rate of AEs was the same for Valeriana and Silaxan, (0.0054 events / observation day) but was slightly higher for Synalan (0.0260 events / observation day).

All AEs were rated as mild, except the AE gastroenteritis under the treatment with Synalan, which was classified as moderate. Over the entire term of the trial only one AE was assessed as potentially related to the investigational product. In this case stomach pressure after Silexan intake was reported to be possibly related to the IMP. Gastrointestinal complaints are a known side effect of Silexan. None of the AEs was serious.

No safety concerns were detected from the analysis of vital signs (systolic and diastolic blood pressure, pulse rate, body temperature), physical examination and ECG when comparing the recorded data of the screening and the trial termination visit. Vital signs which were observed additionally in the evening of the third day of the IMP treatment during each trial period also showed no safety relevant deviations. Blood and urine parameters were only collected once at screening visit supportively to ensure that the included patients with primary insomnia were otherwise healthy.

All in all, the incidence of AEs was low in all three treatment groups. The rate of AEs was slightly higher in the Synalan group under the combined treatment with Valerian extract and Lavender oil in comparison to the sole administration of Valerian extract and Silexan (Lavender oil) respectively. However, no AE in the Synalan group was judged to be causally related to the intake of the IMP.

CONCLUSION

This monocentric, randomized, double-blind, reference-controlled, 3-period cross-over clinical trial was conducted to assess the effectiveness of a combined treatment with Valerian extract (=Valeriana) and Lavender oil (=Silexan) in patients with inability to fall or stay asleep.

After a screening visit eligible patients were further screened during two PSG screening nights. Patients still eligible after the two PSG screening nights were randomized to one of the six treatment sequences (Synalan-Silexan-Valeriana, Valeriana-Synalan-Silexan, Silexan-Valeriana-Synalan, Synalan-Valeriana-Silexan, Valeriana-Silexan-Synalan, Silexan-Synalan-Valeriana) and received the three treatments for three days according to the respective sequence in three different periods, which were separated by 7-day wash-out phases. At the end of the three-day treatment periods patients were evaluated according to objective (PSG), subjective and subsequent daytime functioning endpoints. After one day of treatment patients were evaluated for a subset of the endpoints (subjective and daytime functioning endpoints). All analyses were done exploratory according to the protocol and statistical analysis plan.

Out of the 175 screened patients, 32 patients were randomized and received at least one dose of trial medication and were therefore included in the safety set. The FAS comprised 31 patients and the PPS consisted of 30 patients. There were slightly more women (58.1%) than men (41.9%) enrolled. The mean age was 34.8 (SD: ±7.78) years, ranging from 23 to 49 years. There was no relevant difference among the sequence groups with regard to the demographic data.

All three treatments [redacted] compared to the screening values (without treatment). Synalan showed [redacted] of the polysomnographic and subjective endpoints compared to Valeriana. The [redacted] for Synalan vs. Valeriana were [redacted] in the polysomnographic endpoints and for [redacted] in the subjective endpoints. For the comparison of the endpoints between Synalan and Silexan treatment [redacted] could be shown regarding all endpoints.

The overall incidence of AEs and the rate of AEs per observation days was low during all three active treatments and the subsequent respective 3-day risk phase. There was no accumulation of AEs with regard to SOCs and PTs. The rate of AEs was slightly higher in the Synalan group with combined treatment compared to the sole administration of Valeriana and Silexan

respectively. However, no AE in the Synalan group was assessed to be causally related to the intake of the IMP.

All AEs were rated as mild, except for one AE, which was classified as moderate (under Synalan). Only one expected AE was assessed to be potentially related to the IMP after intake of Silexan. None of the AEs was serious.

No safety concern with respect to one of the three IMPs was detected from the analysis of vital signs, physical examination and ECG.

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