Clinical and biometrical study report

SYNOPSIS

Multi-center, double-blind, randomized, reference-controlled study to prove the efficacy, safety and tolerability of Lavender oil WS® 1265 / Silexan *(Lavandula angustifolia)* in patients with Generalized Anxiety Disorder

Results of the interim and final analysis

Schwabe Study No. 750201.01.016

EudraCT No. 2006-000521-61

Date of report: 16 February 2012

First subject included: 30 May 2007

Last subject completed (first study part): 09 November 2010

SYNOPSIS

Sponsor:	Dr. Willmar Schwabe & Co. KG, Karlsruhe, Germany
Study title:	Multi-center, double-blind, randomized, reference-controlled study to prove the efficacy, safety and tolerability of Lavender oil WS® 1265 (Lavandula angustifolia) in patients with Generalized Anxiety Disorder
Relevant amendments:	Amd. 1: modification of inclusion/exclusion criteria; update of Paroxetine contraindications, drug interactions, precautions; inclusion of a safety visit in week 1 and a reduced laboratory in week 2; analysis of efficacy with regard to gender. Amd. 3: modification of inclusion/exclusion criteria; exclusion of sleep disturbances; inclusion of the Physician Withdrawal checklist. Amd. 4: increase of participating centers. Amd 6: inclusion of a 4th study arm with 160 mg WS® 1265.
Principal Investigator according to ICH-GCP:	Prof. Dr. med. habil.
Investigators, centres of the first study part until the interim analysis:	The study was conducted in 57 study centres in Germany.
Study period of the first study part:	First subject included: 30 May 2007 Last subject completed (first study part): 09 November 2010 End of first study part (interim analysis): 13 April 2011
Publications:	None
Clinical phase:	III

Objectives:

Primary objective:

To prove the efficacy of Lavender oil WS® 1265 (= Silexan) as compared to placebo in the treatment of patients with generalized anxiety disorder.

The change of the HAM-A total score between baseline and week 10 is compared between the treatment groups and used as the primary outcome variable.

Secondary objectives:

- To compare the responder and remitter rates between the treatment groups whereby responders and remitters are defined as: at least 50 % reduction of the HAM-A total score between baseline and week 10 (response). Total score of the HAM-A below 10 at week 10 (remission).

- To compare paroxetine and placebo, and Lavender oil WS® 1265 and paroxetine with regard to the primary and secondary efficacy variables.

Methodology:

A treatment-free run-in period (three to seven days) was followed by a ten weeks double-blind treatment period with either 80 mg Lavender oil WS® 1265 sid or 160 mg Lavender oil WS® 1265 sid or 20 mg paroxetine sid or placebo. Afterwards a one week down-titration phase was planned. The primary outcome variable was the intra-individual change in the HAM-A total score from baseline to week 10.

Number of subjects included in the interim analysis:

	Planned to be randomized (interim analysis)	Patients taken into account for the interim analysis				
				Safety	Efficacy	
		Included	Randomized	Safety analysis set	Full analysis set	Per protocol set
Placebo	134		137	136	135	114
Silexan 80 mg	134		136	135	135	119

Silexan 160 mg	129		129	128	121	103
Paroxetine	134		137	137	132	114
All	531	616	539	536	523	450

Source data: appendix listing 16.2.I.2.2 and table 16.2.II.2.2

Diagnosis and main criteria for inclusion:

Patients included were men or women (aged 18 to 65 years) with a primary diagnosis of Generalized Anxiety Disorder (GAD) according to ICD-10 (F41.1) / DSM-IV (300.02) treated by a general practitioner or a specialized physician. In order to be eligible for study inclusion, all patients were required to have a HAM-A total score ≥ 18 and item 1 *anxious mood* ≥ 2 and item 2 *tension* ≥ 2 and HAM-A subscore *psychic anxiety* ≤ 21, and a Covi Anxiety Scale total score ≥ 9 at baseline. Patients were not allowed to have had any axis I diagnosis (except the study indication GAD) or a current or recent history of major depression within 6 months before study entry. Patients were excluded either if they had predominant and/or severe depressive symptoms (HAMD item 1 “depressed mood” ≥ 2, HAMD total score > 17, Raskin Depression Scale total score > 7), had a risk of suicide (HAMD item 3 “suicide” ≥ 2), a history or evidence of substance dependence (sedatives, hypnotics and anxiolytics within the last 6 months before the study), had schizophrenia, or had currently used other psychotropic drugs within 30 days of baseline visit.

Test preparation, dose and mode of administration, batch number:

Run-in phase (3 - 7 days): no treatment

Double-blind treatment phase (day 1 - day 70; 10 weeks):

Patients of the Lavender oil 80 mg group received one capsule containing 80 mg of Lavender oil (SMC 7563, batch no. 0200702 / 0200811 / 0200904) and one capsule paroxetine placebo (SMC 9041P, batch no. 0200602 / 0200801).

Patients of the Lavender oil 160 mg group received one capsule containing 160 mg of Lavender oil (SMC 7570, batch

no. 0200812 / 0200905) and one capsule paroxetine placebo (SMC 9041P, batch no. 0200602 / 0200801).

Down-titration phase (day 71 to day 77; 1 week):

Patients of the Lavender oil 80 mg and 160 mg group received one capsule Lavender oil placebo (SMC 7563P, batch no. 0200701 / 0200810 / 0200903) and one capsule paroxetine placebo (SMC 9041P, batch no. 0200602 / 0200801) on days 2, 4, 6, and 8 (reserve).

Control preparation, dose and mode of administration, batch number:

Run-in phase (3 - 7 days): no treatment

Double-blind treatment phase (day 1 - day 70; 10 weeks):

Patients of the placebo group received one capsule Lavender oil placebo (SMC 7563P, batch no. 0200701 / 0200810 / 0200903) and one capsule paroxetine placebo (SMC 9041P, batch no. 0200602 / 0200801).

Patients of the paroxetine group received one capsule paroxetine 20 mg (SMC 9041, batch no. 0200701 / 0200802) and one capsule Lavender oil placebo (SMC 7563P, batch no. 0200701 / 0200810 / 0200903).

Down-titration phase (day 71 to day 77; 1 week):

Patients of the placebo group received one capsule Lavender oil placebo (SMC 7563P, batch no. 0200701 / 0200810 / 0200903) and one capsule paroxetine placebo (SMC 9041P, batch no. 0200602 / 0200801) on days 2, 4, 6, and 8 (reserve).

Patients of the paroxetine group received one capsule Lavender oil placebo (SMC 7563P, batch no. 0200701 / 0200810 / 0200903) and one capsule paroxetine 20 mg (SMC 9041, batch no. 0200701 / 0200802) on days 2, 4, 6, and 8 (reserve).

Duration of treatment: Ten weeks of double-blind treatment, according to the protocol.

Criteria for evaluation: **Primary efficacy variables**:

- Individual difference of HAM-A total score between baseline and end of treatment (week 10 or end of treatment in case of premature study termination)

Secondary efficacy variables:

- Response criteria based on the HAM-A total score, Clinical Global Impressions of severity of disorder, Clinical Global Impressions of change from baseline and Covi Anxiety scale total score
- Individual differences of the following outcome variables between baseline and end of treatment:
  - HAM-A subscores *somatic anxiety* and *psychic anxiety*
  - Single items of the HAM-A Scale
  - Subscales of the Sheehan Disability Scale
  - Subscores of SF-36 for the documentation of quality of life
  - Numerical Analogue Scale
  - Raskin Depression Rating Scale total score
  - Hamilton Rating Scale for Depression
  - Covi Anxiety Scale total score
- Clinical Global Impressions of severity of disorder (CGI - item 1) as an organized global assessment of severity conducted by the investigator
- Clinical Global Impressions of change from baseline (CGI - item 2) as an organized global assessment of change from baseline conducted by the investigator
- Physician Withdrawal Checklist scores for evaluation of symptoms of withdrawal from study medication

Safety:

- Adverse Events
- Laboratory tests

Statistical methods: The test problems were examined using apriori ordered hypotheses to control the experimentwise type I error rate

(Maurer, Horthorn, Lehmacher, 1995). In the first step, it was investigated if Silexan (WS® 1265) 160 mg is superior to placebo. If the corresponding null hypothesis (placebo is at least as effective as Silexan (WS® 1265) 160 mg) could be rejected, the null hypothesis stating no superiority of Silexan 80 mg as compared to placebo could be tested. The null-hypotheses were tested using an analysis of covariance with the factors treatment group and the covariate baseline value of the HAM-A total score. In the interim analysis a null-hypothesis was rejected, if the corresponding p-value was at most $\alpha_1 = 0.0152$ (one-sided) and accepted if the p-value was at least $\alpha_0 = 0.20$ (one-sided) (Bauer and Köhne, 1994). In the final analysis, a null-hypothesis not already rejected in the interim analysis can be rejected, if the product of the corresponding p-values computed from the sample evaluated in the interim analysis (first study part) and from those patients not evaluated in the interim analysis (second study part) is at the most $c_\alpha = 0.0038$. Application of the decision strategy for a-priori ordered hypotheses in studies with an adaptive interim analysis (Kieser, Bauer, Lehmacher, 1999) assures the control of the experimentwise type I error rate $\alpha = 0.025$ (one-sided). The primary analysis was based on the FAS with missing values replaced by the LOCF. Additionally, a per protocol analysis was performed to demonstrate robustness of the results.

Results:

Demographic and anthropometric data (full analysis set)

(sex: absolute (relative) frequency and two-sided chi-square test p-value; age, weight, body mass index: mean ± standard deviation, median and two-sided Kruskal-Wallis test p-value)

		Placebo (N=135)	Silexan 80 mg (N=135)	Silexan 160 mg (N=121)	Paroxetine (N=132)	p-value
Sex	Male	36 (26.7 %)	40 (29.6 %)	32 (26.4 %)	30 (22.7 %)	0.649
	Female	99 (73.3 %)	95 (70.4 %)	89 (73.6 %)	102 (77.3 %)	

Age [y]	44.6±12.3 48.0	45.7±11.5 46.0	47.1±11.8 49.0	45.8±12.4 48.5	0.521
Weight [kg]	74.4±16.3 70.0	74.4±15.9 72.0	78.2±16.8 75.0	75.0±14.8 73.0	0.213
Height [cm]	169.3±9.0 168.0	169.2±9.6 168.5	168.3±9.0 168.0	168.2±8.4 168.0	0.791
BMI [kg/m²]	25.9±4.9 25.0	25.9±4.7 24.9	27.5±5.0 26.7	26.4±4.4 26.1	0.027

Source data: appendix tables 16.2.II.4.1 and 16.2.III.4.1

Demographic and anthropometric data (per protocol set)

(sex: absolute (relative) frequency and two-sided chi-square test p-value; age, weight, body mass index: mean ± standard deviation, median and two-sided Kruskal-Wallis test p-value)

		Placebo (N=114)	**Silexan 80 mg (N=119)**	**Silexan 160 mg (N=103)**	**Paroxetine (N=114)**	**p-value**
Sex	Male	27 (23.7 %)	36 (30.3 %)	29 (28.2 %)	27 (23.7 %)	0.586
	Female	87 (76.3 %)	83 (69.7 %)	74 (71.8 %)	87 (76.3 %)	
Age [y]		45.1±11.9 48.0	45.7±11.5 46.0	47.0±12.2 49.0	45.4±12.3 49.0	0.680
Weight [kg]		74.4±16.7 70.0	74.7±15.2 74.0	78.4±16.9 74.0	75.6±14.8 74.5	0.258
Height [cm]		168.8±9.1 167.5	169.1±9.7 168.0	168.2±9.0 168.0	168.3±8.3 168.0	0.882
BMI [kg/m²]		26.0±5.0 25.0	26.0±4.6 25.1	27.6±5.0 26.7	26.6±4.5 26.3	0.052

Source data: appendix tables 16.2.II.4.1 and 16.2.III.4.1

Efficacy results - primary outcome measure during the course of the trial

Hamilton Rating Scale for Anxiety total score

(mean ± standard deviation, median and p-value of the two-sided t-test; last observation carried forward)

Full analysis set							
	Placebo (N=135)	**Silexan 80 mg (N=135)**	**Silexan 160 mg (N=121)**	**Paroxetine (N=132)**	**p-value**		
					i)	**ii)**	**iii)**

Full analysis set							
	Placebo (N=135)	**Silexan 80 mg (N=135)**	**Silexan 160 mg (N=121)**	**Paroxetine (N=132)**	**p-value i)**	**ii)**	**iii)**
Baseline	25.1±4.7 25.0	25.8±4.8 25.0	26.0±4.5 25.0	25.8±4.9 25.0	0.216	0.120	0.209
Week 10 - Baseline	-9.5±9.0 -9.0	-12.8±8.7 -13.0	-14.1±9.3 -14.0	-11.3±8.0 -10.0	0.002	<0.001	0.096

Per protocol set							
	Placebo (N=114)	**Silexan 80 mg (N=119)**	**Silexan 160 mg (N=103)**	**Paroxetine (N=114)**	**p-value i)**	**ii)**	**iii)**
Baseline	25.2±4.7 25.0	25.9±4.8 25.0	26.0±4.5 25.0	25.7±4.8 25.0	0.284	0.226	0.478
Week 10 - Baseline	-9.8±8.8 -10.0	-13.8±8.0 -14.0	-14.7±9.5 -16.0	-12.1±7.7 -11.0	<0.001	<0.001	0.040

i) 80 mg Silexan vs. placebo; ii) 160 mg Silexan vs. placebo; iii) Paroxetine vs. placebo
Source data: appendix tables 16.2.II.6.2.1, 16.2.III.6.2.1, 16.2.II.6.2.2 and 16.2.III.6.2.2

Results of the confirmatory analysis of the primary efficacy variable "intra-individual difference of HAM-A total score between baseline and week 10"

(Full analysis set; last observation carried forward)

Analysis of Covariance°	**Difference of HAM-A total score between baseline and week 10**		
	Difference between Least Square Means^	95 % confidence intervals for difference between LSMEANS	p-value (one-sided)
Silexan 160 mg - Placebo	-4.0	[-6.1 ; -1.9]	0.0002
Silexan 80 mg - Placebo	-2.8	[-4.8 ; -0.9]	0.0026

° analysis of covariance with factor treatment and the baseline value as covariate
^ a negative difference between LSMEANS indicates better performance or health status under active treatment as compared to placebo
Source data: appendix Tables 16.2.III.6.2.1

Evaluation of the primary efficacy variable "intra-individual difference of HAM-A total score between baseline and week 10"

(Per protocol set; last observation carried forward)

Analysis of Covariance°	Difference of HAM-A total score between baseline and week 10		
	Difference between Least Square Means^	95 % confidence intervals for difference between LSMEANS	p-value (two-sided)
Silexan 160 mg - Placebo	-4.3	[-6.6; -2.0]	0.0003
Silexan 80 mg - Placebo	-3.5	[-5.6; -1.5]	0.0007

° analysis of covariance with factor treatment and the baseline value as covariate
^ a negative difference between LSMEANS indicates better performance or health status under active treatment as compared to placebo
Source data: appendix Tables 16.2.III.6.2.2

Responders and patients with remission

(absolute and relative frequency of patients and two-sided p-value of χ^2-test; last observation carried forward)

	Full analysis set						
	Placebo (N=135)	Silexan 80 mg (N=135)	Silexan 160 mg (N=121)	Paroxetine (N=132)	p-value i)	p-value ii)	p-value iii)
Improvement of HAM-A total score ≥ 50 % at week 10	51 (37.8 %)	70 (51.9 %)	73 (60.3 %)	57 (43.2 %)	0.020	<0.001	0.368
HAM-A total score < 10 at week 10	40 (29.6 %)	45 (33.3 %)	56 (46.3 %)	45 (34.1 %)	0.512	0.006	0.434
HAM-A total score ≤ 7 at week 10	30 (22.2 %)	40 (29.6 %)	46 (38.0 %)	33 (25.0 %)	0.165	0.006	0.593
Improvement of HAM-A total score ≥ 50 % and CGI item 2 ≤ 2 at week 10	44 (32.6 %)	65 (48.1 %)	68 (56.2 %)	50 (37.9 %)	0.007	<0.001	0.263
Improvement of CGI item 1 ≥ 2 categories at week 10	40 (29.6 %)	59 (43.7 %)	62 (51.2 %)	47 (35.6 %)	0.012	<0.001	0.201
CGI item 2 ≤ 2 at week 10	56 (41.5 %)	79 (58.5 %)	79 (65.3 %)	72 (54.5 %)	0.003	<0.001	0.014
CGI item 3.1 ≤ 2 at week 10	61 (45.2 %)	82 (60.7 %)	82 (67.8 %)	81 (61.4 %)	0.003	<0.001	0.001

Full analysis set							
	Placebo (N=135)	Silexan 80 mg (N=135)	Silexan 160 mg (N=121)	Paroxetine (N=132)	p-value i)	p-value ii)	p-value iii)
Improvement of COVI total score ≥ 50 % at week 10	40 (29.6 %)	60 (44.4 %)	71 (58.7 %)	55 (41.7 %)	0.012	<0.001	0.040
COVI total score ≤ 5 at week 10	41 (30.4 %)	60 (44.4 %)	64 (52.9 %)	48 (36.4 %)	0.017	<0.001	0.299

Per protocol set							
	Placebo (N=114)	Silexan 80 mg (N=119)	Silexan 160 mg (N=103)	Paroxetine (N=114)	p-value i)	p-value ii)	p-value iii)
Improvement of HAM-A total score ≥ 50 % at week 10	44 (38.6 %)	66 (55.5 %)	63 (61.2 %)	53 (46.5 %)	0.010	<0.001	0.228
HAM-A total score < 10 at week 10	33 (28.9 %)	43 (36.1 %)	50 (48.5 %)	41 (36.0 %)	0.242	0.003	0.258
HAM-A total score ≤ 7 at week 10	24 (21.1 %)	38 (31.9 %)	44 (42.7 %)	30 (26.3 %)	0.060	<0.001	0.350
Improvement of HAM-A total score ≥ 50 % and CGI item 2 ≤ 2 at week 10	37 (32.5 %)	62 (52.1 %)	59 (57.3 %)	46 (40.4 %)	0.002	<0.001	0.212
Improvement of CGI item 1 ≥ 2 categories at week 10	34 (29.8 %)	56 (47.1 %)	56 (54.4 %)	44 (38.6 %)	0.006	<0.001	0.148
CGI item 2 ≤ 2 at week 10	46 (40.4 %)	74 (62.2 %)	68 (66.0 %)	68 (59.6 %)	<0.001	<0.001	0.003
CGI item 3.1 ≤ 2 at week 10	51 (44.7 %)	77 (64.7 %)	72 (69.9 %)	77 (67.5 %)	<0.001	<0.001	<0.001
Improvement of COVI total score ≥ 50 % at week 10	33 (28.9 %)	58 (48.7 %)	62 (60.2 %)	51 (44.7 %)	0.002	<0.001	0.013
COVI total score ≤ 5 at week 10	35 (30.7 %)	58 (48.7 %)	55 (53.4 %)	44 (38.6 %)	0.005	<0.001	0.210

i) 80 mg Silexan vs. placebo; ii) 160 mg Silexan vs. placebo; iii) Paroxetine vs. placebo;
Source data: appendix tables 16.2.II.6.2.1, 16.2.III.6.2.1, 16.2.II.6.2.2, and 16.2.III.6.2.2

Secondary efficacy measures (full analysis set)

Baseline value and score change between baseline and week 10 (N, mean ± standard deviation, median, two-sided t-test p-values; full analysis set; last observation carried forward)

		Placebo	Silexan 80 mg	Silexan 160 mg	Paroxetine	p-value i)	p-value ii)	p-value iii)
Hamilton Rating Scale for Anxiety - Subscore I Somatic anxiety	Baseline	135 11.3±3.8 12.0	135 11.7±3.6 12.0	121 11.7±3.1 11.0	132 11.4±3.7 11.5	0.335	0.254	0.696
	Week 10 - Baseline	135 -4.5±4.8 -4.0	135 -5.9±4.4 -6.0	121 -6.5±4.4 -7.0	132 -4.5±4.3 -4.0	0.015	<0.001	0.919
Hamilton Rating Scale for Anxiety - Subscore II Psychic anxiety	Baseline	135 13.8±2.6 14.0	135 14.1±2.7 14.0	121 14.2±2.6 14.0	132 14.4±2.6 14.5	0.383	0.213	0.085
	Week 10 - Baseline	135 -5.0±5.0 -5.0	135 -7.0±5.0 -7.0	121 -7.7±5.4 -8.0	132 -6.7±4.7 -7.0	0.001	<0.001	0.004
Covi Anxiety Scale - Total score	Baseline	135 10.8±1.4 11.0	135 10.7±1.4 10.0	121 11.2±1.6 11.0	132 10.9±1.3 11.0	0.722	0.030	0.540
	Week 10 - Baseline	135 -3.5±2.8 -3.0	135 -4.4±2.9 5.0	121 -5.2±3.1 -6.0	132 -4.0±2.7 -4.0	0.009	<0.001	0.117
Numerical Analogue Scale (Restlessness/ anxiety)	Baseline	135 7.5±1.4 8.0	135 7.5±1.3 8.0	121 7.7±1.4 8.0	132 7.6±1.3 8.0	0.837	0.205	0.499
	Week 10 - Baseline	135 -2.5±2.6 -2.0	135 -3.4±2.7 -3.0	121 -4.0±2.9 -4.0	132 -3.0±2.5 -3.0	0.007	<0.001	0.134
Clinical Global Impression - Item 1 *severity of disorder*	Baseline	135 4.6±0.6 5.0	135 4.7±0.6 5.0	121 4.6±0.7 5.0	132 4.6±0.6 5.0	0.300	0.684	0.582
	Week 10 - Baseline	133 -1.0±1.3 -1.0	131 -1.5±1.3 -1.0	119 -1.8±1.5 -2.0	125 -1.3±1.3 -1.0	0.005	<0.001	0.102
Clinical Global Impression - Item 2 *change from baseline*	Week 10	130 2.8±1.3 3.0	129 2.3±1.1 2.0	116 2.1±1.1 2.0	123 2.4±1.2 2.0	<0.001	<0.001	0.014
Sheehan Disability Scale - Global impairment (total score)	Baseline	135 18.2±6.2 18.0	135 18.1±7.0 18.0	121 20.3±5.7 20.0	132 18.5±6.8 19.0	0.883	0.006	0.700
	Week 10 - Baseline	133 -5.0±7.4 -3.0	131 -7.1±8.1 -6.0	118 -8.5±8.9 -7.0	125 -7.2±7.4 -6.0	0.026	<0.001	0.017
SF-36 Summary measures score - Physical	Baseline	135 54.2±22.2 52.8	135 54.1±22.1 54.0	121 49.7±20.2 46.3	132 53.7±19.3 52.3	0.944	0.093	0.823

		Placebo	Silexan 80 mg	Silexan 160 mg	Paroxetine	p-value i)	p-value ii)	p-value iii)
health	Week 10 - Baseline	133 9.2±18.1 3.8	131 13.4±19.9 8.8	118 19.0±22.0 14.6	125 13.1±19.5 8.8	0.073	<0.001	0.095
SF-36 Summary measures score - Mental health	Baseline	135 36.7±18.1 32.3	135 35.4±18.5 32.1	121 31.4±17.1 28.6	132 33.8±19.4 28.9	0.587	0.019	0.210
	Week 10 - Baseline	133 14.4±23.5 7.4	131 22.3±24.5 17.5	118 28.2±26.8 24.9	125 22.5±22.8 19.1	0.008	<0.001	0.006

i) 80 mg Silexan vs. placebo; ii) 160 mg Silexan vs. placebo; iii) Paroxetine vs. placebo
Source data: appendix tables 16.2.II.6.2.1 and 16.2.III.6.2.1

Secondary efficacy measures (per protocol set)

Baseline value and score change between baseline and week 10 (N, mean ± standard deviation, median, two-sided t-test p-values; full analysis set; last observation carried forward)

		Placebo	Silexan 80 mg	Silexan 160 mg	Paroxetine	p-value i)	p-value ii)	p-value iii)
Hamilton Rating Scale for Anxiety - Subscore I Somatic anxiety	Baseline	114 11.4±3.8 12.0	119 11.7±3.7 12.0	103 11.7±3.1 11.0	114 11.4±3.6 11.0	0.537	0.551	0.986
	Week 10 - Baseline	114 -4.6±4.6 -4.0	119 -6.2±4.2 -6.0	103 -6.7±4.5 -7.0	114 -4.9±4.3 -4.5	0.004	<0.001	0.533
Hamilton Rating Scale for Anxiety - Subscore II Psychic anxiety	Baseline	114 13.9±2.7 14.0	119 14.2±2.7 14.0	103 14.3±2.5 14.0	114 14.3±2.6 14.0	0.296	0.172	0.211
	Week 10 - Baseline	114 -5.2±4.9 -5.0	119 -7.5±4.5 -8.0	103 -8.0±5.5 -9.0	114 -7.1±4.6 -7.0	<0.001	<0.001	0.003
Covi Anxiety Scale - Total score	Baseline	114 10.9±1.4 11.0	119 10.8±1.4 11.0	103 11.4±1.6 11.0	114 10.9±1.3 11.0	0.603	0.012	0.627
	Week 10 - Baseline	114 -3.6±2.8 -3.0	119 -4.7±2.7 -5.0	103 -5.3±3.1 -6.0	114 -4.3±2.5 -5.0	0.002	<0.001	0.029
Numerical Analogue Scale (Restlessness/	Baseline	114 7.6±1.4 8.0	119 7.5±1.3 8.0	103 7.8±1.3 8.0	114 7.7±1.1 8.0	0.948	0.186	0.558

		Placebo	Silexan 80 mg	Silexan 160 mg	Paroxetine	p-value i)	p-value ii)	p-value iii)
anxiety)	Week 10 - Baseline	114 -2.5±2.6 -2.0	119 -3.7±2.6 -3.5	103 -4.2±3.0 -4.2	114 -3.2±2.4 -3.1	0.001	<0.001	0.049
Clinical Global Impression - Item 1 *severity of disorder*	Baseline	114 4.6±0.6 5.0	119 4.6±0.7 5.0	103 4.6±0.7 5.0	114 4.6±0.6 5.0	0.553	0.566	0.757
	Week 10 - Baseline	114 -1.0±1.3 -1.0	118 -1.5±1.4 -1.0	103 -1.9±1.5 -2.0	113 -1.4±1.3 -1.0	0.004	<0.001	0.050
Clinical Global Impression - Item 2 *change from baseline*	Week 10	111 2.8±1.3 3.0	116 2.2±1.0 2.0	100 2.1±1.1 2.0	111 2.4±1.1 2.0	<0.001	<0.001	0.011
Sheehan Disability Scale - Global impairment (total score)	Baseline	114 18.6±6.2 19.0	119 18.0±6.9 18.0	103 20.6±5.8 21.0	114 18.3±6.8 19.0	0.502	0.015	0.699
	Week 10 - Baseline	114 -5.2±7.5 -3.0	118 -7.7±8.1 -6.0	103 -8.8±9.3 -7.0	113 -7.4±7.1 -6.0	0.019	0.002	0.030
SF-36 Summary measures score - Physical health	Baseline	114 54.2±22.2 53.6	119 55.2±22.3 56.0	103 49.6±19.8 46.0	114 54.5±19.3 52.9	0.740	0.110	0.922
	Week 10 - Baseline	114 9.0±18.1 3.6	118 14.0±19.3 8.8	103 20.0±21.8 15.8	113 13.5±19.9 8.8	0.043	<0.001	0.074
SF-36 Summary measures score - Mental health	Baseline	114 36.0±18.4 31.5	119 35.5±18.2 32.5	103 31.1±16.6 27.9	114 34.4±20.1 28.9	0.853	0.042	0.534
	Week 10 - Baseline	114 14.7±23.4 7.5	118 23.6±24.4 18.9	103 29.9±27.5 26.7	113 23.1±22.8 20.3	0.005	<0.001	0.007

i) 80 mg Silexan vs. placebo; ii) 160 mg Silexan vs. placebo; iii) Paroxetine vs. placebo
Source data: appendix tables 16.2.II.6.2.2 and 16.2.III.6.2.2

Safety analysis

Adverse events

Number and incidence of adverse events (any causality; safety analysis set)

Treatment	Study period	Patients in study	Patients (%) with adverse events	Observation days	Number of adverse events	Events per observation days
Placebo	Run-in phase	136	4 (2.9 %)	1129	4	0.004
	Active treatment phase	136	42 (30.9 %)	8765	73	0.008
	Down titration phase[1)]	116	2 (1.7 %)	821	2	0.002
	≥ 3 days after end of down titration phase	136	1 (0.7 %)		2	
Silexan 80 mg	Run-in phase	135	1 (0.7 %)	1027	2	0.002
	Active treatment phase	135	47 (34.8 %)	8604	71	0.008
	Down titration phase[1)]	122	3 (2.5 %)	814	3	0.004
	≥ 3 days after end of down titration phase	135	1 (0.7 %)		1	
Silexan 160 mg	Run-in phase	128	2 (1.6 %)	1051	2	0.002
	Active treatment phase	128	32 (25.0 %)	7752	48	0.006
	Down titration phase[1)]	109	0 (0.0 %)	796	0	0.000
	≥ 3 days after end of down titration phase	128	0 (0.0 %)		0	
Paroxetine	Run-in phase	137	9 (6.6 %)	1033	10	0.010
	Active treatment phase	137	56 (40.9 %)	8157	89	0.011
	Down titration phase[1)]	110	4 (3.6 %)	775	4	0.005
	≥3 days after end of down titration phase	137	0 (0.0 %)		0	

[1)] Beginning to 2 days after end of down titration phase
Source data: appendix table 16.2.II.7.1.1

Intensity and causality of adverse events with begin during the active treatment phase (safety analysis set, Placebo, N=136)

(absolute and relative frequency of subjects)

Intensity	Mild		Moderate		Severe		
	Suspected*		Suspected*		Suspected*		
System Organ Class	Yes	No	Yes	No	Yes	No	Total
- TOTAL -	8 (5.9)	21 (15.4)	9 (6.6)	14 (10.3)	1 (0.7)	1 (0.7)	42 (30.9)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Eye disorders	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	2 (1.5)
Gastrointestinal disorders	4 (2.9)	3 (2.2)	4 (2.9)	1 (0.7)	0 (0.0)	0 (0.0)	11 (8.1)
General disorders and administration site conditions	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Infections and infestations	0 (0.0)	17 (12.5)	2 (1.5)	3 (2.2)	0 (0.0)	1 (0.7)	21 (15.4)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)
Metabolism and nutrition disorders	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Musculoskeletal and connective tissue disorders	0 (0.0)	2 (1.5)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	4 (2.9)
Nervous system disorders	2 (1.5)	3 (2.2)	3 (2.2)	3 (2.2)	1 (0.7)	0 (0.0)	12 (8.8)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	2 (1.5)
Reproductive system and breast disorders	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	2 (1.5)
Surgical and medical procedures	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)
Vascular disorders	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)

Intensity	Mild		Moderate		Severe		
	Suspected*		Suspected*		Suspected*		
System Organ Class	Yes	No	Yes	No	Yes	No	Total

* All assessments except 'not related' were classified as suspected adverse events (i.e. causal relationship probable , possible or unlikely)
Source data: appendix table 16.2.II.7.1.3

Intensity and causality of adverse events with begin during the active treatment phase (safety analysis set, Silexan 80 mg, N=135)

(absolute and relative frequency of subjects and subject identification)

Intensity	Mild		Moderate		Severe		
	Suspected*		Suspected*		Suspected*		
System Organ Class	Yes	No	Yes	No	Yes	No	Total
- TOTAL -	9 (6.7)	20 (14.8)	8 (5.9)	12 (8.9)	2 (1.5)	1 (0.7)	47 (34.8)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Ear and labyrinth disorders	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Eye disorders	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Gastrointestinal disorders	8 (5.9)	2 (1.5)	6 (4.4)	2 (1.5)	1 (0.7)	0 (0.0)	17 (12.6)
Infections and infestations	0 (0.0)	8 (5.9)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	11 (8.1)
Injury, poisoning and procedural complications	0 (0.0)	2 (1.5)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	3 (2.2)
Investigations	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Musculoskeletal and connective tissue disorders	1 (0.7)	2 (1.5)	0 (0.0)	5 (3.7)	0 (0.0)	0 (0.0)	8 (5.9)
Nervous system disorders	3 (2.2)	4 (3.0)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)	10 (7.4)
Psychiatric disorders	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	3 (2.2)
Respiratory, thoracic and mediastinal disorders	1 (0.7)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	3 (2.2)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.7)	1 (0.7)	2 (1.5)	0 (0.0)	0 (0.0)	4 (3.0)

Intensity	Mild		Moderate		Severe		
	Suspected*		Suspected*		Suspected*		
System Organ Class	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Total**

* All assessments except 'not related' were classified as suspected adverse events (i.e. causal relationship probable , possible or unlikely)
Source data: appendix table 16.2.II.7.1.3

Intensity and causality of adverse events with begin during the active treatment phase (safety analysis set, Silexan 160 mg, N=128)

(absolute and relative frequency of subjects and subject identification)

Intensity	Mild		Moderate		Severe		
	Suspected*		Suspected*		Suspected*		
System Organ Class	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Total**
- TOTAL -	10 (7.8)	7 (5.5)	9 (7.0)	5 (3.9)	2 (1.6)	2 (1.6)	32 (25.0)
Eye disorders	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Gastrointestinal disorders	6 (4.7)	0 (0.0)	8 (6.3)	1 (0.8)	1 (0.8)	1 (0.8)	16 (12.5)
General disorders and administration site conditions	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Infections and infestations	0 (0.0)	6 (4.7)	0 (0.0)	2 (1.6)	0 (0.0)	1 (0.8)	9 (7.0)
Investigations	1 (0.8)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.8)
Nervous system disorders	2 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	3 (2.3)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.6)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)	2 (1.6)
Reproductive system and breast disorders	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)

Intensity	Mild		Moderate		Severe		
	Suspected*		Suspected*		Suspected*		
System Organ Class	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Total**
Surgical and medical procedures	0 (0.0)	1 (0.8)	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)	3 (2.3)

* All assessments except 'not related' were classified as suspected adverse events (i.e. causal relationship probable , possible or unlikely)
Source data: appendix table 16.2.II.7.1.3

Intensity and causality of adverse events with begin during the active treatment phase (safety analysis set, Paroxetine, N=137)

(absolute and relative frequency of subjects and subject identification)

Intensity	Mild		Moderate		Severe		
	Suspected*		Suspected*		Suspected*		
System Organ Class	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Total**
- TOTAL -	18 (13.1)	21 (15.3)	14 (10.2)	9 (6.6)	3 (2.2)	1 (0.7)	56 (40.9)
Eye disorders	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Gastrointestinal disorders	10 (7.3)	6 (4.4)	7 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	22 (16.1)
General disorders and administration site conditions	4 (2.9)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (3.6)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Immune system disorders	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.5)
Infections and infestations	1 (0.7)	10 (7.3)	0 (0.0)	4 (2.9)	0 (0.0)	0 (0.0)	15 (10.9)
Injury, poisoning and procedural complications	0 (0.0)	2 (1.5)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	3 (2.2)
Investigations	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	2 (1.5)
Nervous system disorders	3 (2.2)	3 (2.2)	4 (2.9)	3 (2.2)	1 (0.7)	0 (0.0)	14 (10.2)
Psychiatric disorders	1 (0.7)	0 (0.0)	3 (2.2)	0 (0.0)	2 (1.5)	0 (0.0)	6 (4.4)

Intensity	Mild		Moderate		Severe		
	Suspected*		Suspected*		Suspected*		
System Organ Class	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Total**
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)
Skin and subcutaneous tissue disorders	4 (2.9)	3 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (5.1)
Vascular disorders	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)

* All assessments except 'not related' were classified as suspected adverse events (i.e. causal relationship probable , possible or unlikely)
Source data: appendix table 16.2.II.7.1.3

Adverse events potentially related to study medication

Number and incidence of adverse events potentially related to study medication (safety analysis set)

Treatment group	Study period	Patients in study	Patients with adverse events	Observation days	Number of adverse events	Events per observation day
Placebo	Begin - end of active treatment	136	17	8765	25	0.003
	Down titration phase	116	1	821	1	0.001
Silexan 80 mg	Begin - end of active treatment	135	16	8604	25	0.003
	Down titration phase	122	1	814	1	0.001
Silexan 160 mg	Begin - end of active treatment	128	20	7752	29	0.004
	Down titration phase	109	0	796	0	0.000
Proxetin	Begin - end of active treatment	137	29	8157	49	0.006
	Down titration phase	110	2	775	2	0.003

Incidence was calculated based on exposure days.
Source data: appendix table 16.2.II.7.2.1

Serious adverse events (safety analysis set)

Study period	Treatment group	Patients with SAE	SAEs	ADR
Run-in period		0		
Active treatment	**Placebo**	0		
	Silexan 80 mg	1	Anxiety disorder	No
	Silexan 160 mg	2	Rectal hemorrhage	No
			Suicide attempt	No
	Paroxetine	1	Anxiety	Yes
Down titration[1)]		0		
After down titration	**Placeo**	0		
	Silexan 80 mg	1	Visual impairment	No
	Silexan 160 mg	0		

[1)]Beginning to 2 days after end of down titration phase.

Source data: appendix table 16.2.II.7.3.2 and table 16.2.II.7.4.2

Results of the Physician Withrawal Scale - week 10 value and score change between week 10 and week 11 (per protocol set for analysis of PWC)

(mean ± standard deviation, median; p-value of the two-sided t-test for the comparison of active drugs to placebo at week 10 and two-sided p-value of the ANCOVA with factor treatment and value at week 10 as covariate for comparing changes (wek 11 – week 10) between the former active treatment groups and placebo; last observation carried forward)

		Placebo (N=105)	Silexan 80 mg (N=115)	Silexan 160 mg (N=97)	Paroxetine (N=101)	p-value i)	p-value ii)	p-value iii)
Total score	Week 10	11.43±10.79 8.00	7.53±7.41 6.00	6.65±9.67 3.00	8.80±7.87 8.00	0.002	0.001	0.048
	Week 11 - Week 10	-0.19±4.20 0.00	-0.23±3.81 0.00	-0.65±4.93 0.00	-0.51±4.47 0.00	0.728	0.103	0.385
Total number of symptoms	Week 10	7.57±5.61 7.00	5.61±4.32 5.00	4.68±5.16 3.00	6.50±5.02 6.00	0.004	<0.001	0.149
	Week 11 - Week 10	-0.31±2.47 0.00	-0.40±2.62 0.00	-0.25±2.84 0.00	-0.55±2.60 0.00	0.369	0.318	0.266

i) 80 mg Silexan vs. placebo; ii) 160 mg Silexan vs. placebo; iii) Paroxetine vs. placebo
Source data: appendix tables 16.2.II.6.2.2 and 16.2.III.6.2.2

Conclusion

This multi-center, randomized, double-blind, placebo- and reference-controlled parallel-group study with double-dummy administration of study medication was conducted to confirm the clinical efficacy, safety and tolerability of Lavender oil WS® 1265 in the treatment of patients with Generalized Anxiety Disorder (GAD). A treatment-free run-in period (three to seven days) was followed by a ten weeks double-blind acute treatment period. During the ten weeks of randomized double-blind treatment patients received either 80 mg Lavender oil WS® 1265 sid or 160 mg Lavender oil WS® 1265 sid or 20 mg paroxetine sid, or placebo. Afterwards, a one week double-blind down titration resp. withdrawal phase was performed. In this phase the patients of the paroxetine group received 20 mg paroxetine every second day and the patients of the Lavender oil groups as well as the patients of the placebo group received placebo.

It was planned to include 531 men or women, 18 to 65 years old with a diagnosis of GAD. This study report describes the results of the pre-planned interim analysis. The statistical procedure applied in the interim analysis was specified in the clinical trial protocol dated 15

May 2006, and protocol amendment No. 6, dated 26 August 2008. A statistical analysis plan specifying the analysis sets and details of the evaluation was prepared on 15 March 2011 before breaking the blind.

The primary outcome variable for the analysis was the intra-individual difference of the HAM-A total score between baseline and end of treatment (week 10 or end of individual treatment in case of premature study termination). Secondary outcome variables were the rate of patients with Hamilton Rating Scale for Anxiety (HAM-A) total score reduction of at least 50 % after week 10 of treatment (responder) and the rate of patients with HAM-A total score below ten points at week 10 (remitter). Further secondary outcome variables were the changes of the HAM-A subscores and single items, the components of the Covi anxiety scale, Numerical Analogue Scale, Clinical Global Impressions scale, Sheehan Disability Anxiety Scale, and the 36 Item Short Form Health Survey. In addition, the following response criteria were defined: HAM-A total score below 7 points at end of treatment (strong remitter), improvement of HAM-A total score of at least 50 % and CGI item 2 (change from baseline) at least 2 at end of treatment (much improved), CGI item 2 at least 2 at end of treatment, CGI item 3.1 (therapeutic effect) at least 2 at end of treatment (moderate improvement), improvement of COVI total score of at least 50 % between baseline and end of treatment, COVI total score of 5 points at end of treatment. All mentioned variables were compared between the active treatment groups (Silexan (WS® 1265) 80 mg and 160 mg, and paroxetine) and placebo.

All patients who received randomized study medication at least once were analyzed with regard to safety measures (safety analysis set [SAF]). The primary analysis of efficacy was based on the full analysis set, which included all patients of the SAF who had at least one measure of the primary efficacy parameter (HAM-A total score) during active treatment period after baseline visit and patients who terminated the study prematurely because of lack of efficacy or an AE, for which a causal relationship to study medication could not be excluded. The per protocol set (PPS) consisted of all patients of the FAS without any relevant protocol violation and patients who terminated the study prematurely due to a reason related to efficacy or an AE, for which a causal relationship to study medication could not be excluded. In order to assess the impact of drop outs on efficacy results, the subset of observed cases (OC) was evaluated for the FAS and the PPS. The subset of OC included

only data from patients who did not discontinue prematurely and were available for evaluation at the designated assessment visits.

In this interim analysis a total of 536 treated patients (placebo: 136 patients, Silexan (WS® 1265) 80 mg: 135 patients, Silexan (WS® 1265) 160 mg: 128 patients, paroxetine: 137 patients) could be evaluated in the safety analysis set. Thirteen (13) of the SAF patients did not have at least one assessment of primary efficacy parameters (HAM-A total score) after baseline during acute treatment phase and did not terminate the study prematurely due to lack of efficacy or an AE causally related to study medication. Therefore, the FAS comprised 523 patients (placebo: 135 patients, Silexan (WS® 1265) 80 mg: 135 patients, Silexan (WS® 1265) 160 mg: 121 patients, paroxetine: 132 patients). The PPS consisted of 450 patients (placebo: 114 patients, Silexan (WS® 1265) 80 mg: 119 patients, Silexan (WS® 1265) 160 mg: 103 patients, paroxetine: 114 patients). In the following, the results of the FAS are described. A total of 385 (73.6 %) patients were women and 138 (26.4 %) were men. The fraction of women and men was comparable in all four treatment groups (females: placebo: 99 [73.3 %] patients, Silexan (WS® 1265) 80 mg: 95 [70.4 %] patients, Silexan (WS® 1265) 160 mg: 89 [73.6 %] patients, paroxetine: 102 [77.3 %] patients; p = 0.649, p-value of the two-sided chi-square test).

GAD was diagnosed on average 2 to 3 years before participation in the study (placebo: 2.6±4.7 years, Silexan (WS® 1265) 80 mg. 2.3±5.0 years, Silexan (WS® 1265) 160 mg: 2.8±5.3 years, paroxetine: 2.3±4.1 years ago) and the present anxiety episode lasted about one year (placebo: 1.1±1.4 years, Silexan (WS® 1265) 80 mg: 1.0±1.1 years, Silexan (WS® 1265) 160 mg: 1.1±1.5 years, paroxetine: 1.0±1.8 years). Both, duration of GAD and duration of present anxiety episode were comparable between the three active treatment groups and placebo at the beginning of the study.

At baseline, the mean HAM-A total score was between 25 and 26 for all treatment groups (placebo: 25.1±4.7, Silexan (WS® 1265) 80 mg: 25.8±4.8, Silexan (WS® 1265) 160 mg: 26.0±4.5, paroxetine: 25.8±4.9) and hence comparable between the three active treatment groups and placebo.

Patients randomized to be treated with Silexan (WS® 1265) 80 mg and with paroxetine were comparable to patients of the placebo group regarding baseline assessment of all secondary

efficacy measures. There were no relevant differences concerning the baseline values of the HAM-A subscores, the Numerical Analogue Scale (NAS) and item 1 "*severity of disorder"* of the CGI for the Silexan (WS® 1265) 160 mg group as compared to placebo. But patients of the Silexan (WS® 1265) 160 mg group reported slightly more severe symptoms of anxiety assessed by the COVI total score and more severly global impairment assessed by the Sheehan Disability Scale. Furthermore, the SF-36 summary measure scores for *physical health* and *mental health* indicated an on average worse health on baseline for patients of the Silexan (WS® 1265) 160 mg group than for patients of the placebo group.

In the confirmatory analysis, the null-hypothesis stating no superiority of the treatment with Silexan (WS® 1265) 160 mg as compared to placebo with respect to the primary outcome variable (intra-individual difference of the total score of the HAM-A between baseline and end of treatment) could be rejected (p=0.0002, p-value from ANCOVA with factor treatment and HAM-A total score at baseline as covariate, one-sided, significance level $\alpha_1 = 0.0152$ for the interim analysis). The second null-hypothesis stating no superiority of Silexan (WS® 1265) 80 mg treatment compared to placebo could be rejected either (p=0.0026, one-sided, significance level $\alpha_1 = 0.0152$ for the interim analysis). Therefore, the objective of the study was achieved already with the current interim analysis and the study will not be continued. Since the recruitment was stopped for preparing the interim analysis there was no over-run. Hence, this interim analysis constitutes the final analysis of the study and no further patients will be recruited or treated. The evaluation of the PPS revealed similar results as the confirmatory analysis of the FAS. Furthermore, the results based on observed cases confirmed the results based on the last observation carried forward for the FAS and PPS.

During the double-blind treatment period the HAM-A total score of 73 (60.3 %) patients of the Silexan (WS® 1265) 160 mg group, 70 (51.9 %) patients of the Silexan (WS® 1265) 80 mg group, 57 (43.2 %) patients of the paroxetine group and 51 (37.8 %) patients treated with placebo was reduced by at least 50 % (responder). The differences between the Silexan (WS® 1265) treatment groups compared to placebo were statistically significant (p-values of the two-sided χ^2-test: Silexan (WS® 1265) 160 mg vs. placebo: p<0.001, Silexan (WS® 1265) 80 mg vs. placebo: p=0.020). The proportion of patients with remission (HAM-A total score below ten) was higher in the Silexan (WS® 1265) 160 mg group (56 [46.3 %]

patients) than in the other three treatment groups (placebo: 40 [29.6 %] patients, Silexan (WS® 1265) 80 mg: 45 [33.3 %] patients, paroxetine: 45 [34.1 %] patients; p-value of the two-sided χ^2-test: Silexan (WS® 1265) 160 mg vs. placebo: p=0.006). Strong remission (i.e. HAM-A total score less or equal than seven at week 10) was found in 46 (38.0 %) patients treated with Silexan (WS® 1265) 160 mg, in 40 (29.6 %) patients treated with Silexan (WS® 1265) 80 mg, in 33 (25.0 %) patients treated with paroxetine, and in 30 (22.2 %) patients treated with placebo. The difference between the Silexan (WS® 1265) 160 mg treatment group and placebo was statistically significant (two-sided χ^2-test: p=0.006). Statistically significantly more patients in the Silexan (WS® 1265) treatment groups (160 mg and 80 mg) than in the placebo group had an improvement of HAM-A total score of at least 50 % and a *CGI item 2 changes from baseline lower or equal two* at week 10 (placebo: 44 [32.6 %] patients, Silexan (WS® 1265) 80 mg: 65 [48.1 %] patients, Silexan (WS® 1265) 160 mg: 68 [56.2 %] patients, paroxetine: 50 [37.9 %] patients; p-values of the two-sided χ^2-test: Silexan (WS® 1265) 80 mg vs. placebo: p=0.007, Silexan (WS® 1265) 160 mg vs. placebo: p<0.001). For all response criteria based only on the CGI the proportion of patients fulfilling the respective criterion was statistically significantly higher in the Silexan (WS® 1265) treatment groups (160 mg, and 80 mg) than in the placebo group. Similarly, clearly more patients treated with paroxetine than patients treated with placebo fulfilled the defined criteria. The comparisons of the paroxetine group to placebo were statistically significant for the criteria *CGI item 2 at most two at week 10* and *CGI item 3.1 at most two at week 10* (p = 0.003 and p < 0.001, respectively, p-values of the two-sided χ^2-test). At week 10 for 71 (58.7 %) of patients treated with Silexan (WS® 1265) 160 mg, for 60 (44.4 %) of the patients treated with Silexan (WS® 1265) 80 mg, for 55 (41.7 %) of the patients treated with paroxetine and for 40 (29.6 %) of the patients treated with placebo the COVI total score had improved by at least 50 %. For all three active treatment groups statistically significantly more patients showed an improvement of at least 50 % of the COVI total score than under placebo treatment (p-values of the two-sided χ^2-test: Silexan (WS® 1265) 80 mg vs. placebo: p=0.012, Silexan (WS® 1265) 160 mg vs. placebo: p<0.001, paroxetine vs. placebo: p=0.040). Statistically significantly less patients treated with placebo showed a COVI total score of at most five at week 10 compared to patients treated with Silexan (WS® 1265) (placebo: 41 [30.4 %] patients, Silexan (WS® 1265) 80 mg: 60 [44.4 %] patients, Silexan (WS® 1265) 160 mg: 64 [52.9 %] patients; p-values of the two-sided χ^2-test: Silexan (WS® 1265) 80 mg vs. placebo: p=0.017, Silexan (WS® 1265) 160 mg vs. placebo: p<0.001).

Slightly more patients treated with paroxetine than patients treated with placebo had a COVI total score of at most five at week 10 (placebo: 41 [30.4 %] patients, paroxetine: 48 [36.4 %] patients; p-value of the two-sided χ^2-test: paroxetine vs. placebo: p=0.299).

During the double-blind treatment period both subscores of the HAM-A showed statistically significantly higher improvements under both Silexan (WS® 1265) treatments compared to placebo (*somatic anxiety:* placebo: -4.5±4.8, Silexan (WS® 1265) 80 mg: -5.9±4.4, Silexan (WS® 1265) 160 mg: -6.5±4.4; p-values of the two-sided t-test: Silexan (WS® 1265) 80 mg vs. placebo: p=0.015; Silexan (WS® 1265) 160 mg vs. placebo: p<0.001; *psychic anxiety*: placebo: -5.0±5.0, Silexan (WS® 1265) 80 mg: -7.0±5.0, Silexan (WS® 1265) 160 mg: -7.7±5.4 ; p-values of the two-sided t-test: Silexan (WS® 1265) 80 mg vs. placebo: p=0.001, Silexan (WS® 1265) 160 mg vs. placebo: p<0.001). Under paroxetine treatment the subscore *psychic anxiety* showed a statistically significant higher improvement than under placebo, the changes of the subscore *somatic anxiety* were comparable between these treatment groups (*somatic anxiety*: placebo: -4.5±4.8, paroxetine: -4.5±4.3; p=0.919, p-value of the two-sided t-test; *psychic anxiety*: placebo: -5.0±5.0, paroxetine: -6.7±4.7; p=0.004, p-value of the two-sided t-test).

During ten weeks of double-blind treatment the Numerical Analogue Scale (NAS) declined by 4.0±2.9 in patients treated with Silexan (WS® 1265) 160 mg, by 3.4±2.7 in patients treated with Silexan (WS® 1265) 80 mg, by 3.0±2.5 in patients treated with paroxetine, and by 2.5±2.6 in patients treated with placebo. Comparing the changes under Silexan (WS® 1265) treatment and under placebo treatment, both differences between the Silexan (WS® 1265) treatment groups and the placebo group were statistically significant (p-values of the two-sided t-test: Silexan (WS® 1265) 80 mg vs. placebo: p=0.007, Silexan (WS® 1265) 160 mg vs. placebo: p<0.001).

Considering the Clinical Global Impressions (CGI) at the end of the double-blind treatment period item 1 had improved on average by 1.8±1.5 in patients treated with Silexan (WS® 1265) 160 mg, by 1.5±1.3 in patients treated with Silexan (WS® 1265) 80 mg, by 1.3±1.3 in patients treated with paroxetine, and by 1.0±1.3 in patients treated with placebo. The improvement of *severity of disorder* in both Silexan (WS® 1265) treatment groups were statistically significantly higher than that in the placebo group (p-values of the two-sided t-test: Silexan (WS® 1265) 80 mg vs. placebo: p=0.005, Silexan (WS® 1265) 160 mg vs.

placebo: p<0.001). Item 2 *change from baseline* confirmed the improvement in all four treatment groups. The best change was found in patients treated with Silexan (WS® 1265) 160 mg (2.1±1.1), the worst in patients treated with placebo (2.8±1.3). Comparing the three active treatment groups to placebo revealed statistically significantly lower mean values (i.e. better change) for item 2. At week 10, the *therapeutic effect* (item 3.1) was rated between 1.9±1.0 and 2.1±1.0 under Silexan (WS® 1265) 80 mg, Silexan (WS® 1265) 160 mg and paroxetine treatment. Patients treated with placebo showed a statistically significantly higher rating (i.e. lower effect) for the *therapeutic effect.*

After ten weeks of double-blind treatment, the highest reduction of impairment in all three aspects of daily life was observed in patients treated with Silexan (WS® 1265) 160 mg (impairment of work: -3.0±3.4; impairment of social life: -2.8±3.2; impairment of family life: -2.7±3.3; global impairment: -8.5±8.9); the lowest reduction of impairment was reported in patients treated with placebo (impairment of work: -1.8±2.7; impairment of social life: -1.6±2.9; impairment of family life: -1.6±2.8; global impairment: -5.0±7.4). The reduction in patients treated with Silexan (WS® 1265) 80 mg and with paroxetine was similar (impairment of work: Silexan (WS® 1265) 80 mg: -2.3±3.1, paroxetine: -2.3±2.6; impairment of social life: Silexan (WS® 1265) 80 mg: -2.4±2.9, paroxetine: -2.4±2.9; impairment of family life/home: Silexan (WS® 1265) 80 mg: -2.5±2.9, paroxetine: -2.5±2.7; global impairment: Silexan (WS® 1265) 80 mg: -7.1±8.1, paroxetine: -7.2±7.4). Except for the reduction of impairment of work, the reduction of impairment was statistically significantly higher in the active treatment groups than in the placebo group.

For both summary measure scores *physical health* and *mental health* patients treated in any of the three active treatment groups (Silexan (WS® 1265) 80 mg, Silexan (WS® 1265) 160 mg, paroxetine) showed a higher improvement after ten weeks of double-blind treatment than patients treated with placebo. Patients under Silexan (WS® 1265) 160 mg treatment had improved most; patients under Silexan (WS® 1265) 80 mg and paroxetine treatment had a similar improvement. Differences were statistically significant when comparing the Silexan (WS® 1265) 160 mg group to the placebo group (average reduction in summary measure score *physical health*: Silexan (WS® 1265) 160 mg: 19.0±22.0, placebo: 9.2±18.1, p< 0.001, p-value of the two-sided t-test, average reduction in summary measure score *mental health*: Silexan (WS® 1265) 160 mg: 28.2±26.8, placebo: 14.4±23.5, p< 0.001, p-value of the two-sided t-test).

During the active treatment period 42 (30.9 %) patients of the placebo group experienced 73 adverse events (AE), 47 (34.8 %) patients of the Silexan (WS® 1265) 80 mg group experienced 71 AEs, 32 (25.0 %) patients of the Silexan (WS® 1265) 160 mg group experienced 48 AEs, and 56 (40.9 %) patients of the paroxetine group experienced 89 AEs. Most AEs were of mild or moderate intensity. The number of AEs per observation day was similar in the placebo and in the two Silexan (WS® 1265) groups whereas it was slightly higher in the paroxetine group. On the level of system organ classes no statistically relevant higher event rate could be observed for one of the Silexan treatment groups as compared to the placebo group. In the paroxetine group an 8 % higher event rate (risk difference) than in the placebo group was found for gastrointestinal disorders. Eructation, a known side effect of Silexan (WS® 1265) was the only adverse event that appeared with a relevantly higher rate under Silexan (WS® 1265) than in patients exposed to placebo or paroxetine. Vertigo, constipation, and fatigue were observed more often in patients treated with paroxetine as compared to the Silexan (WS® 1265) groups and the placebo group.

At least one adverse event potentially related to study medication was experienced during the active treatment period by 17 (12.5 %) patients of the placebo group (25 AEs), by 16 (11.9 %) patients of the Silexan (WS® 1265) 80 mg group (25 AEs), by 20 (15.6 %) patients of the Silexan (WS® 1265) 160 mg group (29 AEs), and by 29 (21.2 %) patients of the paroxetine group (49 AEs). The placebo and the Silexan (WS® 1265) treatment groups were similar with respect to the number of potentially related adverse events per observation day between begin and end of active treatment whereas the paroxetine treatment group tended to show more potentially related adverse events per observation day. In the following system organ classes according to the MedDRA system more potentially related adverse events were documented for patients treated with paroxetine than in the Silexan (WS® 1265) groups: general disorders, nervous system disorders, psychiatric disorders and skin and subcoutanous tissue disorders. Apart from eructation no meaningful increases in incidence rates of adverse drug reactions (ADR) were observed in the Silexan (WS® 1265) treatment groups as compared to placebo. A statistically relevant higher incidence of fatigue was observed for patients treated with paroxetine than in the Silexan (WS® 1265) groups.

Four non-fatal serious adverse events occurred during the active treatment period (Silexan (WS® 1265) 80 mg: 1 SAE; Silexan (WS® 1265) 160mg: 2 SAEs; Paroxetine: 1 SAE). All three SAEs reported for patients treated with Silexan (WS® 1265) were assessed as not

related to the investigational treatment. For one SAE in the paroxetine group (aggravation of anxiety) a causal relationship relationship could not be excluded, since anxiety and depersonalisation are rare expected ADRs of paroxetine.

During the down titration period potential withdrawal symptoms could not be observed for patients treated with Silexan (WS® 1265) before.

In summary, the null-hypothesis stating no superiority of treatment with Silexan (WS® 1265) 160 mg as compared to placebo with respect to the intra-individual difference of the total score of the HAM-A between baseline and end of treatment could be rejected. The second null-hypothesis stating no superiority of treatment with Silexan (WS® 1265) 80 mg treatment as compared to placebo could be rejected either. Therefore, the objective of the study was achieved already with the current interim analysis and the study will not be continued. This interim analysis constitutes the final analysis of the study and no further patients will be recruited or treated. These results were confirmed in the PPS. In addition, patients treated with paroxetine showed clearly higher improvement of GAD during the ten weeks double-blind treatment phase compared to patients treated with placebo, in particular in the analysis of observed cases (assay sensitivity). As expected due to known adverse drug reactions, slightly more patients treated with paroxetine than patients from one of the other treatment groups discontinued the study prematurely.

Overall, patients treated with paroxetine tended to have more AEs as well as adverse drug reactions compared to patients treated with placebo or Silexan (WS® 1265). Silexan as well as paroxetine had no harmful influence on laboratory measures, physical findings and vital signs. Silexan (WS® 1265) was well tolerated in both dosages 80 mg and 160 mg.