Clinical trial results:
Multi-center, double-blind, placebo-controlled, randomized phase IIIb study to prove the efficacy, safety and tolerability of Silexan (WS®1265) in patients with mixed anxiety and depressive disorder (ICD-10, F41.2).

Summary

EudraCT number	2012-000438-21
Trial protocol	DE
Global end of trial date	08 July 2014

Results information

Result version number	v1 (current)
This version publication date	01 March 2016
First version publication date	25 July 2015

Trial information

Trial identification

Sponsor protocol code	750201.01.035

Additional study identifiers

ISRCTN number	ISRCTN65844716
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 May 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 May 2014
Global end of trial reached?	Yes
Global end of trial date	08 July 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to prove the efficacy of Silexan in the treatment of patients with mixed anxiety and depressive disorder in comparing the change of the HAMA total score and the MADRS total score between baseline and Week 10 between Silexan and placebo.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 348
Worldwide total number of subjects	348
EEA total number of subjects	348

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	348
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Thirty patients were not randomized and did not receive the investigational product since they did not fulfill all in-/exclusion criteria or withdrew informed consent.

Pre-assignment period milestones

Number of subjects started	348
Number of subjects completed	318

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 11
Reason: Number of subjects	Protocol deviation: 16
Reason: Number of subjects	Patients decision: 3

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Silexan

Arm description:

Investigational medical product containing Silexan, 80 mg, one additional Patient was randomized and started Treatment but had no post-baseline measurements of the primary efficacy parameter (HAMA-A total score and MADRS total score) during the randomized ten-week treatment period.

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

Dosage and administration details:

1 x 80 mg daily

Arm title	Placebo

Arm description:

Placebo, two additional Patients were randomized and started Treatment but had no post-baseline measurements of the primary efficacy parameter (HAMA-A total score and MADRS total score) during the randomized ten-week treatment period.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

1 x 1 capsule daily

Number of subjects in period 1[1]	Silexan	Placebo
Started	160	158
Completed	145	145
Not completed	15	13
private reasons	3	-
Consent withdrawn by subject	4	4
Adverse event, non-fatal	1	1
Patients decision	-	1
Lost to follow-up	1	-
Lack of efficacy	6	7

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Silexan: Investigational medical product Silexan, 80 mg, one additional Patient was randomized and started Treatment but had no post-baseline measurements of the primary efficacy parameter (HAMA-A total score and MADRS total score) during the randomized ten-week treatment period.
Placebo, two additional Patients were randomized and started Treatment but had no post-baseline measurements of the primary efficacy parameter (HAMA-A total score and MADRS total score) during the ran

Baseline characteristics

Reporting groups

Reporting group title	Silexan

Reporting group description:

Investigational medical product containing Silexan, 80 mg, one additional Patient was randomized and started Treatment but had no post-baseline measurements of the primary efficacy parameter (HAMA-A total score and MADRS total score) during the randomized ten-week treatment period.

Reporting group title	Placebo

Reporting group description:

Placebo, two additional Patients were randomized and started Treatment but had no post-baseline measurements of the primary efficacy parameter (HAMA-A total score and MADRS total score) during the randomized ten-week treatment period.

Reporting group values	Silexan	Placebo	Total
Number of subjects	160	158	318
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	160	158	318
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	47.5	47.8	
standard deviation	± 12.8	± 12.8	-
Gender categorical Units: Subjects			
Female	106	113	219
Male	54	45	99

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full analysis set (FAS) included all patients who received the investigational medical product (Silexan or placebo) at least once and had at least one measure of one of the primary efficacy parameters (HAMA total score or MADRS 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 the investigational product could not be excluded (even if these patients had no efficacy measurement during active treatment period)

Reporting group values	Full analysis set		
Number of subjects	315		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	315		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	47.8		
standard deviation	± 12.6		
Gender categorical Units: Subjects			
Female	218		
Male	97		

End points

End points reporting groups

Reporting group title	Silexan

Reporting group description:

Investigational medical product containing Silexan, 80 mg, one additional Patient was randomized and started Treatment but had no post-baseline measurements of the primary efficacy parameter (HAMA-A total score and MADRS total score) during the randomized ten-week treatment period.

Reporting group title	Placebo

Reporting group description:

Placebo, two additional Patients were randomized and started Treatment but had no post-baseline measurements of the primary efficacy parameter (HAMA-A total score and MADRS total score) during the randomized ten-week treatment period.

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The Full analysis set (FAS) included all patients who received the investigational medical product (Silexan or placebo) at least once and had at least one measure of one of the primary efficacy parameters (HAMA total score or MADRS 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 the investigational product could not be excluded (even if these patients had no efficacy measurement during active treatment period)

Primary: Change of HAMA total score between baseline and end of treatment

End point title	Change of HAMA total score between baseline and end of treatment

End point description:

End point type	Primary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-10.8 (± 9.6)	-8.4 (± 8.9)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA with factor treatment, center and the respective baseline total score value as covariate, LOCF Method was used.

Comparison groups	Silexan v Placebo

Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0077 [1]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-2.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.471
upper limit	-0.477

Notes:

[1] - one sided p-value

Primary: Change of MADRS total score between baseline and end of treatment

End point title	Change of MADRS total score between baseline and end of treatment

End point description:

End point type	Primary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-9.2 (± 9.9)	-6.1 (± 7.6)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

ANCOVA with factor treatment, center and the respective baseline total score value as covariate, LOCF Method was used.

Comparison groups	Placebo v Silexan
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [2]
Method	ANCOVA
Parameter estimate	LS mean difference
Point estimate	-3.25

Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.144
upper limit	-1.362

Notes:

[2] - one sided p-value

Secondary: Change of HAMA Subscore Somatic Anxiety

End point title	Change of HAMA Subscore Somatic Anxiety

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-4.2 (± 4.4)	-3.1 (± 4.4)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.11
upper limit	-0.14

Secondary: Change of HAMA Subscore Physic Anxiety

End point title	Change of HAMA Subscore Physic Anxiety

End point description:

End point type	Secondary
End point timeframe:	
Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-6.6 (± 5.7)	-5.3 (± 5.1)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.51
upper limit	-0.1

Secondary: HAMA total score improvement >= 50 %	
End point title	HAMA total score improvement >= 50 %
End point description:	
HAMA total score improvement >= 50 percent between baseline and week 10	
End point type	Secondary
End point timeframe:	
Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Subjects	66	54		

Statistical analyses

Statistical analysis title	Chi square test
Statistical analysis description: LOCF, two sided	
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.208 [3]
Method	Chi-squared

Notes:
[3] - two sided

Secondary: HAMA total score < 10

End point title	HAMA total score < 10
End point description:	
End point type	Secondary
End point timeframe: End of Treatment (week 10)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Subjects	55	45		

Statistical analyses

Statistical analysis title	Chi square test
Statistical analysis description: LOCF, two-sided	
Comparison groups	Silexan v Placebo

Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.273 [4]
Method	Chi-squared

Notes:
[4] - two-sided

Secondary: Change of HAMA Item 2 (tension)

End point title	Change of HAMA Item 2 (tension)

End point description:

End point type	Secondary

End point timeframe:
Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-1.2 (± 1.2)	-0.9 (± 1.2)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	-0.01

Secondary: Change of HAMA Item 14 (Behavior at interview)

End point title	Change of HAMA Item 14 (Behavior at interview)

End point description:

End point type	Secondary
End point timeframe:	
Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-0.7 (± 1)	-0.5 (± 0.9)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	-0.02

Secondary: MADRS total score improvement >= 50 %

End point title	MADRS total score improvement >= 50 %
End point description:	
MADRS total score improvement >= 50 percent between baseline and week 10	
End point type	Secondary
End point timeframe:	
Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Subjects	64	50		

Statistical analyses

Statistical analysis title	Chi square test
Statistical analysis description: LOCF, two-sided	
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [5]
Method	Chi-squared

Notes:
[5] - two-sided

Secondary: MADRS total score < =10

End point title	MADRS total score < =10
End point description: Remission: MADRS total score <=10 at week 10	
End point type	Secondary
End point timeframe: End of Treatment (week 10)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Subjects	74	53		

Statistical analyses

Statistical analysis title	Chi square test
Statistical analysis description: LOCF, two-sided	
Comparison groups	Silexan v Placebo

Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.023 [6]
Method	Chi-squared

Notes:
[6] - two-sided

Secondary: Change of STAI X1 (state anxiety) score

End point title	Change of STAI X1 (state anxiety) score

End point description:

End point type	Secondary

End point timeframe:
Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-7.8 (± 13.5)	-6.6 (± 12)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.424
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-1.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.99
upper limit	1.68

Secondary: Change of STAI X2 (trait anxiety) score

End point title	Change of STAI X2 (trait anxiety) score

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-6.9 (± 11.7)	-6.1 (± 10)		

Statistical analyses

Statistical analysis title	ANOVA
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.496
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.25
upper limit	1.58

Secondary: Sheehan disability scale: Impairment (Work/School/University)

End point title	Sheehan disability scale: Impairment (Work/School/University)

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-1.7 (± 3.8)	-0.9 (± 3.1)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description: LOCF	
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.037
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.62
upper limit	-0.05

Secondary: Sheehan disability scale: Impairment (Social Life)

End point title	Sheehan disability scale: Impairment (Social Life)
End point description:	
End point type	Secondary
End point timeframe: Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-1.6 (± 3.1)	-0.8 (± 2.6)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description: LOCF	
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.015
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	-0.16

Secondary: Sheehan disability scale: Impairment (Family Life / Home Responsibilities)

End point title	Sheehan disability scale: Impairment (Family Life / Home Responsibilities)
End point description:	
End point type	Secondary
End point timeframe: Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-1.9 (± 3)	-0.7 (± 2.6)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description: LOCF	
Comparison groups	Silexan v Placebo

Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.78
upper limit	-0.54

Secondary: Sheehan disability scale: Global Impairment

End point title	Sheehan disability scale: Global Impairment

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-5.1 (± 8.5)	-2.3 (± 6.6)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

LOCF

Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-2.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.49
upper limit	-1.08

Secondary: SF 36 total scores: Physical Health

End point title	SF 36 total scores: Physical Health

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	12.9 (± 25)	6.3 (± 16.7)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

LOCF

Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	6.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.87
upper limit	11.4

Secondary: SF 36 total scores: Mental Health

End point title	SF 36 total scores: Mental Health

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	20.6 (± 29.5)	11.3 (± 20.3)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

LOCF

Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.73
upper limit	15.06

Secondary: SF 36 individual scores: Physical Functioning

End point title	SF 36 individual scores: Physical Functioning

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	7.3 (± 23.7)	2.9 (± 17.3)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description: LOCF	
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	4.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.17
upper limit	9.11

Secondary: SF 36 individual scores: Role-Physical

End point title	SF 36 individual scores: Role-Physical
End point description:	
End point type	Secondary
End point timeframe: Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	20.2 (± 46.5)	11.9 (± 39.3)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description: LOCF	
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.091
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	8.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.33
upper limit	17.95

Secondary: SF 36 individual scores: Bodily Pain	
End point title	SF 36 individual scores: Bodily Pain
End point description:	
End point type	Secondary
End point timeframe: Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	12.3 (± 31.1)	6.1 (± 23)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description: LOCF	
Comparison groups	Silexan v Placebo

Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	6.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	12.34

Secondary: SF 36 individual scores: General Health

End point title	SF 36 individual scores: General Health

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	11.9 (± 20.8)	4.4 (± 16)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

LOCF

Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	7.56

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.41
upper limit	11.71

Secondary: SF 36 individual scores: Vitality

End point title	SF 36 individual scores: Vitality

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	17.2 (± 26.8)	10 (± 17.3)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

LOCF

Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	7.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	12.31

Secondary: SF 36 individual scores: Social Functioning

End point title	SF 36 individual scores: Social Functioning

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	18.9 (± 32.9)	10.7 (± 23.9)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

LOCF

Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.75
upper limit	14.65

Secondary: SF 36 individual scores: Role-Emotional

End point title	SF 36 individual scores: Role-Emotional

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	30.1 (± 48.3)	15.2 (± 42.3)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description: LOCF	
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	14.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.79
upper limit	25.12

Secondary: SF 36 individual scores: Mental Health

End point title	SF 36 individual scores: Mental Health
End point description:	
End point type	Secondary
End point timeframe: Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	16.5 (± 25.9)	9.2 (± 19.3)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description:	
LOCF	
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	7.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.21
upper limit	12.43

Secondary: CGI tem 1: Severity of Illness

End point title	CGI tem 1: Severity of Illness
End point description:	
End point type	Secondary
End point timeframe:	
Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	154		
Units: Points				
arithmetic mean (standard deviation)	-1.1 (± 1.5)	-0.7 (± 1.2)		

Statistical analyses

Statistical analysis title	Non-parametric analysis
Statistical analysis description:	
LOCF, two-sided, end of Treatment (10 week Treatment period)	
Comparison groups	Silexan v Placebo

Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.008 [7]
Method	Wilcoxon (Mann-Whitney)

Notes:
[7] - two-sided

Secondary: CGI Item 2: Global Improvement

End point title	CGI Item 2: Global Improvement

End point description:

End point type	Secondary

End point timeframe:
End of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	154		
Units: Points				
arithmetic mean (standard deviation)	2.7 (± 1.3)	3.1 (± 1.2)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:
LOCF, two-sided

Comparison groups	Silexan v Placebo
Number of subjects included in analysis	309
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:
[8] - two-sided

Secondary: CGI Item 3.1: Therapeutic Effect

End point title	CGI Item 3.1: Therapeutic Effect

End point description:

End point type	Secondary

End point timeframe:
End of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	154	153		
Units: Points				
arithmetic mean (standard deviation)	2.4 (± 1.2)	2.9 (± 1.1)		

Statistical analyses

Statistical analysis title	Non-parametric analysis
Statistical analysis description: LOCF, two-sided	
Comparison groups	Placebo v Silexan
Number of subjects included in analysis	307
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [9]
Method	Wilcoxon (Mann-Whitney)

Notes:
[9] - two-sided

Secondary: Hospital anxiety and depression scale (HADS) total score

End point title	Hospital anxiety and depression scale (HADS) total score
End point description:	
End point type	Secondary
End point timeframe: Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-4.8 (± 9.5)	-3.8 (± 7.5)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description: LOCF	

Comparison groups	Placebo v Silexan
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.313
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.87
upper limit	0.92

Secondary: Hospital anxiety and depression scale (HADS) anxiety score

End point title	Hospital anxiety and depression scale (HADS) anxiety score

End point description:

End point type	Secondary

End point timeframe:

Baseline and end of Treatment (10 week Treatment period)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-2.6 (± 5.1)	-2 (± 3.9)		

Statistical analyses

Statistical analysis title	ANOVA

Statistical analysis description:

LOCF

Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.21
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-0.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.65
upper limit	0.36

Secondary: Hospital anxiety and depression scale (HADS) depression score

End point title	Hospital anxiety and depression scale (HADS) depression score
End point description:	

End point type	Secondary
End point timeframe:	
Baseline and end of Treatment (10 week Treatment period)	

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Points				
arithmetic mean (standard deviation)	-2.2 (± 5)	-1.8 (± 4.1)		

Statistical analyses

Statistical analysis title	ANOVA
Statistical analysis description:	
LOCF	
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.524
Method	t-test, 2-sided
Parameter estimate	mean difference (change from baseline)
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.35
upper limit	0.69

Secondary: CGI Item 1 Improvement by >= 2 categories at week 10

End point title	CGI Item 1 Improvement by >= 2 categories at week 10

End point description:

End point type	Secondary

End point timeframe:
End of Treatment (week 10)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Subjects	55	27		

Statistical analyses

Statistical analysis title	Chi square test

Statistical analysis description:
LOCF, two-sided

Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [10]
Method	Chi-squared

Notes:
[10] - two-sided

Secondary: CGI Item 2 <= 2 at week 10

End point title	CGI Item 2 <= 2 at week 10

End point description:

End point type	Secondary

End point timeframe:
End of Treatment (week 10)

End point values	Silexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	159	156		
Units: Subjects	74	48		

Statistical analyses

Statistical analysis title	Chi square test
Statistical analysis description: LOCF, two-sided	
Comparison groups	Silexan v Placebo
Number of subjects included in analysis	315
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0029 [11]
Method	Chi-squared

Notes:

[11] - two-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 10 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17

Reporting groups	
Reporting group title	No active treatment
Reporting group description: No active treatment	
Reporting group title	Silexan
Reporting group description: Verum treatment	
Reporting group title	Placebo
Reporting group description: Placebo treatment	

Serious adverse events	No active treatment	Silexan	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 318 (0.31%)	1 / 160 (0.63%)	2 / 158 (1.27%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 318 (0.00%)	1 / 160 (0.63%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 318 (0.31%)	0 / 160 (0.00%)	0 / 158 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			

subjects affected / exposed	0 / 318 (0.00%)	0 / 160 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	0 / 318 (0.00%)	0 / 160 (0.00%)	1 / 158 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	No active treatment	Silexan	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 318 (0.63%)	20 / 160 (12.50%)	15 / 158 (9.49%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 318 (0.63%)	4 / 160 (2.50%)	9 / 158 (5.70%)
occurrences (all)	2	5	10
Gastrointestinal disorders			
Eructation			
subjects affected / exposed	0 / 318 (0.00%)	16 / 160 (10.00%)	0 / 158 (0.00%)
occurrences (all)	0	16	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 318 (0.00%)	3 / 160 (1.88%)	8 / 158 (5.06%)
occurrences (all)	0	4	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 October 2012	Amendment No. 2 extended the validity of the exclusion criterion "MADRS item 10 ≥ 2" from screening and baseline visit to the whole course of the trial. Subjects with a score ≥ 2 for item 10 in a visit had to discontinue treatment with the investigational product.
18 October 2012	Amendment No. 1 comprised a clarification in wording regarding some details of the pre-planned interim analysis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported