



## 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:

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**Results analysis stage**

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|  |              |
|--|--------------|
| 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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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

Notes:

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**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     |
| <b>Arm title</b>             | 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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 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:<br>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:<br>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<br>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<br>Units: years                     |         |         |       |
| arithmetic mean                                    | 47.5    | 47.8    |       |
| standard deviation                                 | ± 12.8  | ± 12.8  | -     |
| Gender categorical<br>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:<br>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<br>Units: Subjects                    |                   |  |  |
| In utero  | 0                 |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                 |  |  |
| Newborns (0-27 days)                                  | 0                 |  |  |
| Infants and toddlers (28 days-23<br>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<br>Units: years                        |                   |  |  |
| arithmetic mean                                       | 47.8              |  |  |
| standard deviation                                    | ± 12.6            |  |  |
| Gender categorical<br>Units: Subjects                 |                   |  |  |
| Female  | 218               |  |  |
| Male  | 97                |  |  |

## End points

### End points reporting groups

|  |                   |
|--|-------------------|
| Reporting group title  | Silexan           |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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 <sup>[1]</sup> |
| 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 <sup>[2]</sup> |
| 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 ( $\pm$ 5.7) | -5.3 ( $\pm$ 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 $\geq$ 50 %

|   |  |
|---|--|
| End point title   | HAMA total score improvement $\geq$ 50 % |
| End point description:  |  |
| HAMA total score improvement $\geq$ 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:<br>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 <sup>[3]</sup> |
| Method   | Chi-squared            |
| Notes:<br>[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:<br>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:<br>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 <sup>[4]</sup> |
| 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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:<br>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 <sup>[5]</sup> |
| Method   | Chi-squared           |
| Notes:<br>[5] - two-sided                            |                       |

## Secondary: MADRS total score < =10

| End point title  | MADRS total score < =10 |
|--|-------------------------|
| End point description:<br>Remission: MADRS total score <=10 at week 10 |                         |
| End point type   | Secondary               |
| End point timeframe:<br>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:<br>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 <sup>[6]</sup> |
| 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) |           |

| <b>End point values</b>              | Silexan            | Placebo          |  |  |
|--------------------------------------|--------------------|------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group  |  |  |
| Number of subjects analysed          | 159                | 156              |  |  |
| Units: Points                        |                    |                  |  |  |
| arithmetic mean (standard deviation) | -6.9 ( $\pm$ 11.7) | -6.1 ( $\pm$ 10) |  |  |

### Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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:<br>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:<br>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

|   |  |
|---|--|
| <b>Statistical analysis title</b>         | ANOVA                                  |
| Statistical analysis description:<br>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:<br>Baseline and end of Treatment (10 week Treatment period) |  |

|                                      |                 |                 |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>              | 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

|   |                   |
|---|-------------------|
| <b>Statistical analysis title</b>         | ANOVA             |
| Statistical analysis description:<br>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 ( $\pm$ 29.5) | 11.3 ( $\pm$ 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 ( $\pm$ 23.7) | 2.9 ( $\pm$ 17.3) |  |  |

## Statistical analyses

| Statistical analysis title                | ANOVA                                  |
|---|--|
| Statistical analysis description:<br>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:<br>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 ( $\pm$ 46.5) | 11.9 ( $\pm$ 39.3) |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>         | ANOVA                                  |
| Statistical analysis description:<br>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:<br>Baseline and end of Treatment (10 week Treatment period) |                                      |

|                                      |                 |                 |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>              | 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

|   |                   |
|---|-------------------|
| <b>Statistical analysis title</b>         | ANOVA             |
| Statistical analysis description:<br>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 ( $\pm$ 26.8) | 10 ( $\pm$ 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:<br>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:<br>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

|   |  |
|---|--|
| <b>Statistical analysis title</b>         | ANOVA                                  |
| Statistical analysis description:<br>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:<br>Baseline and end of Treatment (10 week Treatment period) |                                |

|                                      |                 |                 |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>              | 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

|   |                         |
|---|-------------------------|
| <b>Statistical analysis title</b>   | Non-parametric analysis |
| Statistical analysis description:<br>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 <sup>[7]</sup>  |
| 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 <sup>[8]</sup>  |
| 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 ( $\pm$ 1.2) | 2.9 ( $\pm$ 1.1) |  |  |

## Statistical analyses

| Statistical analysis title                           | Non-parametric analysis |
|--|-------------------------|
| Statistical analysis description:<br>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 <sup>[9]</sup>  |
| Method   | Wilcoxon (Mann-Whitney) |
| Notes:<br>[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:<br>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 ( $\pm$ 9.5) | -3.8 ( $\pm$ 7.5) |  |  |

## Statistical analyses

| Statistical analysis title                | ANOVA |
|---|-------|
| Statistical analysis description:<br>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 <sup>[10]</sup> |
|---------|-------------------------|

|        |             |
|--------|-------------|
| 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

|   |                          |
|---|--------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[11]</sup> |
| 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 %

| <b>Non-serious adverse events</b>                     | 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 $\geq 2$ " from screening and baseline visit to the whole course of the trial. Subjects with a score $\geq 2$ 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported