# Clinical trial results:
# NEUPRO OL, Efficacy profile of Neurexan® in an experimental acute stress setting – an explorative open-label study in healthy probands

## Summary

| | |
|---|---|
| EudraCT number | 2012-002359-40 |
| Trial protocol | DE |
| Global end of trial date | 04 April 2013 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 28 October 2017 |
| First version publication date | 28 October 2017 |
| Summary attachment (see zip file) | C1202 NEUPRO Open label study (Neurexan) (C1202_20131212_C1202_NEUPRO_OL_Synopsis_CSR_03Dec2013_redacted.pdf) |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | C1202 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01703832 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Biologische Heilmittel Heel GmbH |
| Sponsor organisation address | Dr.-Reckeweg-Str. 2-4, Baden-Baden, Germany, 76532 |
| Public contact | Biologische Heilmittel Heel GmbH, Biologische Heilmittel Heel GmbH, +49 7221-501-0, info@heel.com |
| Scientific contact | Biologische Heilmittel Heel GmbH, Biologische Heilmittel Heel GmbH, +49 7221-501-0, info@heel.com |

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 | 04 April 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 04 April 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 April 2013 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective is the efficacy of Neurexan® on tension and nervousness perception using visual analogue scales (VAS) when study participants undergo an emotional stressful condition as compared to natural course. The test method for this study is the TSST protocol.

Protection of trial subjects:

Routine monitoring was performed to verify that rights and well being of participants were protected.

Background therapy:

8 subjects took contraceptives (5 in the Neurexan Group, 3 in the Placebo Group)

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 12 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: 65 |
| Worldwide total number of subjects | 65 |
| EEA total number of subjects | 65 |

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) | 65 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment was carried out in 2 outpatient clinics in Germany (Marburg and Essen).

### Pre-assignment

Screening details:

Telephone pre-screening was carried out and individuals received gross Information about the study. If they were suited for study participation an appointment for the medical and psychological screening was made.
Interested volunteers were invited to the study site for the 1st visit and received oral and written Information about study and ICF.

### Period 1

| | |
|---|---|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Neurexan group |

Arm description:

33 participants were randomized to Neurexan. One premature terminator could not be evaluated for primary efficacy, so 32 participants in the Neurexan group formed the full analysis Set for analysis of efficacy. All randomised subjects were included in the analysis of safety.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Neurexan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

One Neurexan tablet contains: 0.6 mg Avena sativa (dil. D2), 0.6 mg Coffea arabica (dil. D12), 0.6 mg Passiflora incarnata (dil. D2), 0.6 mg Zincum isovalerianum (dil. D4), lactose monohydrate and magnesium stearate
Route of administration: oral
Total administered: 6 tablets (over a period of 2.5 hours - one tablet every 30 minutes)

| | |
|---|---|
| **Arm title** | Natoural course group |

Arm description:

All of the 32 participants randomised to the Natural Course group formed the full analysis set for analysis of efficacy and safety.

| | |
|---|---|
| Arm type | No intervention |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 1** | Neurexan group | Natoural course group |
|---|---|---|
| Started | 33 | 32 |
| Completed | 32 | 32 |
| Not completed | 1 | 0 |
| Consent withdrawn by subject | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Neurexan group |
| Reporting group description: | |
| 33 participants were randomized to Neurexan. One premature terminator could not be evaluated for primary efficacy, so 32 participants in the Neurexan group formed the full analysis Set for analysis of efficacy. All randomised subjects were included in the analysis of safety. | |
| Reporting group title | Natoural course group |
| Reporting group description: | |
| All of the 32 participants randomised to the Natural Course group formed the full analysis set for analysis of efficacy and safety. | |

| Reporting group values | Neurexan group | Natoural course group | Total |
|---|---|---|---|
| Number of subjects | 33 | 32 | 65 |
| 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) | 33 | 32 | 65 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 42.6 | 41.3 | |
| standard deviation | ± 8.4 | ± 8.3 | - |
| Gender categorical<br>Units: Subjects | | | |
| Female | 17 | 17 | 34 |
| Male | 16 | 15 | 31 |
| Ethnic origin<br>Units: Subjects | | | |
| white | 33 | 32 | 65 |
| Body Mass Index (BMI)<br>Units: kg/m2 | | | |
| arithmetic mean | 24.47 | 23.11 | |
| standard deviation | ± 2.76 | ± 2.83 | - |
| Trier Inventory for Chronic Stress - screening scale of chronic stress (SSCS) | | | |
| Includes scores from five scales (chronic worrying, work and social overload, excessive demands and lack of acceptance). | | | |
| Units: score points | | | |
| median | 8 | 9.5 | |
| full range (min-max) | 0 to 19 | 1 to 23 | - |
| Global Severity Index (GSI) of | | | |

| psychological distress | | | |
|---|---|---|---|
| derived from Symptom Checklist 90 | | | |
| Units: score points | | | |
| median | 0.133 | 0.189 | |
| full range (min-max) | 0 to 0.82 | 0 to 1.21 | - |
| Screening height | | | |
| Units: cm | | | |
| arithmetic mean | 175 | 177.2 | |
| standard deviation | ± 9.7 | ± 10.7 | - |
| Screening weight | | | |
| Units: kg | | | |
| arithmetic mean | 75.35 | 73.04 | |
| standard deviation | ± 12.89 | ± 13.81 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Neurexan group |
| Reporting group description: | |
| 33 participants were randomized to Neurexan. One premature terminator could not be evaluated for primary efficacy, so 32 participants in the Neurexan group formed the full analysis Set for analysis of efficacy. All randomised subjects were included in the analysis of safety. | |
| Reporting group title | Natoural course group |
| Reporting group description: | |
| All of the 32 participants randomised to the Natural Course group formed the full analysis set for analysis of efficacy and safety. | |
| Subject analysis set title | Essen Neurexan group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| The secondary endpoint "Change in natural killer (NK) cells" was analysed in the Essen subgroup only. | |
| Subject analysis set title | Essen Natoural course group |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: | |
| The secondary endpoint "Change in natural killer (NK) cells" was analysed in the Essen subgroup only. | |

### Primary: Tension

| | |
|---|---|
| End point title | Tension |
| End point description: | |
| Tension was self-assessed by the participants on a 0 to 100 millimeter (mm) Visual Analogue Scale (VAS), ranging from 0="not at all" to 100="higly", before and after a stress test. The measurements started 30 min before intake of Neurexan or natural course and were repeated until 100 minutes after the end of the stress test.<br>The total stress was then summarized with the Area under the curve (AUC) method. AUC of VAS Tension value was measured from -210 min to +100 min. | |
| End point type | Primary |
| End point timeframe: | |
| 30 min before first intake of Neurexan or natural course until 100 minutes after end of the stress test, i.e.: -210 min, -180 min, -150 min, -120 min, -90 min, -60 min, -30 min, -15 min, 0 min, +15 min, +30 min, +45 min, +60 min, +75 min, +100 min | |

| **End point values** | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 32 | | |
| Units: mm*min | | | | |
| median (full range (min-max)) | 3089.4 (40 to 20940) | 3253.4 (308 to 19305) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Descriptive statistics |
| Statistical analysis description: | |
| Standard descriptive statistics were calculated for continuous variables. All analyses were performed | |

using Version 9.1.3 or later of SAS Software.

| | |
|---|---|
| Comparison groups | Neurexan group v Natoural course group |
| Number of subjects included in analysis | 64 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.1233 |
| Method | ANCOVA |
| Parameter estimate | LS-Mean Difference |
| Point estimate | 752.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -210.6 |
| upper limit | 1715.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 481.2 |

## Primary: Nervousness

| | |
|---|---|
| End point title | Nervousness |

End point description:

Nervousness was self-assessed by the participants on a 0 to 100 millimeter (mm) Visual Analogue Scale (VAS), ranging from 0="not at all" to 100="higly", before and after a stress test. The measurements started 30 min before first intake of Neurexan or natoural course and were repeated until 100 minutes after the end of the stress test.
The total stress was then summarized with the Area under the curve (AUC) method. AUC of VAS Nervousness value was measured from -210 min to +100 min.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

30 min before first intake of Neurexan or natoural course until 100 minutes after end of the stress test, i.e.: -210 min, -180 min, -150 min, -120 min, -90 min, -60 min, -30 min, -15 min, 0 min, +15 min, +30 min, +45 min, +60 min, +75 min, +100 min

| End point values | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 32 | | |
| Units: mm*min | | | | |
| median (full range (min-max)) | 2377.3 (12 to 9071) | 3426.8 (329 to 14898) | | |

## Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Descriptive statistics |

Statistical analysis description:

Standard descriptive statistics were calculated for continuous variables. All analyses were performed using Version 9.1.3 or later of SAS Software.

| | |
|---|---|
| Comparison groups | Neurexan group v Natoural course group |

| | |
|---|---|
| Number of subjects included in analysis | 64 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.5153 |
| Method | ANCOVA |
| Parameter estimate | LS-Mean Difference |
| Point estimate | 334.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -687.6 |
| upper limit | 1356.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 510.7 |

## Secondary: Alpha amylase

| | |
|---|---|
| End point title | Alpha amylase |

End point description:

The stress biomarker salivary alpha amylase was measured before and after a stress test. The measurements started 60 minutes before stress test and were repeated until 100 minutes after the end of the stress test.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

60 minutes before until 100 minutes after stress test, i.e.: -60 min, +15 min, +45 min, +100 min

| End point values | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32[1] | 32 | | |
| Units: IU/ml | | | | |
| median (full range (min-max)) | | | | |
| -60 min | 155.6 (21.6 to 594.86) | 133.2 (11.5 to 591.83) | | |
| +15 min | 242.8 (28.19 to 620.26) | 204.9 (9.82 to 819.87) | | |
| +45 min | 171.3 (21.04 to 786.54) | 138.6 (9.61 to 812.83) | | |
| +100 min | 195.8 (17.35 to 597.39) | 144 (8.02 to 509.27) | | |

Notes:

[1] - Parameter was measured in only 31participants at timepoint -60 min.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Saliva cortisol

| | |
|---|---|
| End point title | Saliva cortisol |

End point description:

The stress biomarker saliva cortisol was measured before and after a stress test. The measurements started 60 minutes before stress test and were repeated until 100 minutes after the end of the stress test.

| End point type | Secondary |
|---|---|

End point timeframe:

60 minutes before until 100 minutes after stress test, i.e.: -60 min, +15 min, +45 min, +100 min

| **End point values** | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32[2] | 32 | | |
| Units: nmol/l | | | | |
| median (full range (min-max)) | | | | |
| -60 min | 7.9 (1.58 to 27.64) | 8.1 (2.84 to 26.39) | | |
| +15 min | 20.3 (2.46 to 121.11) | 19.8 (3.37 to 112.89) | | |
| +45 min | 18.8 (1.22 to 65.42) | 20.6 (2.59 to 33.61) | | |
| +100 min | 8.6 (1.77 to 24.89) | 9.4 (3.44 to 89.56) | | |

Notes:

[2] - Parameter was measured in only 31participants at timepoint -60 min.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Adrenocorticotropic Hormone (ACTH)

| End point title | Adrenocorticotropic Hormone (ACTH) |
|---|---|

End point description:

The stress biomarker Adrenocorticotropic Hormone was measured before and after a stress test. The measurements started 60 minutes before stress test and were repeated until 100 minutes after the end of the stress test.

| End point type | Secondary |
|---|---|

End point timeframe:

60 minutes before until 100 minutes after stress test, i.e.: -60 min, +15 min, +45 min, +100 min

| **End point values** | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31[3] | 24 | | |
| Units: ng/l | | | | |
| median (full range (min-max)) | | | | |
| -60 min | 20.8 (6.07 to 283.81) | 20 (7.95 to 112.99) | | |
| +15 min | 35.4 (13.38 to 116.92) | 31 (11.36 to 158.12) | | |

| | | | | |
|---|---|---|---|---|
| +45 min | 20.4 (9.05 to 55.69) | 20.6 (7.51 to 84.08) | | |
| +100 min | 11.8 (6.99 to 32.99) | 13.7 (3.3 to 31.58) | | |

Notes:

[3] - Parameter was measured in only 30 participants at timepoint -60 min

### Statistical analyses

No statistical analyses for this end point

## Secondary: Epinephrine

| End point title | Epinephrine |
|---|---|

End point description:

The stress biomarker epinephrine (adrenaline) measured before and after a stress test. The measurements started 60 minutes before stress test and were repeated until 100 minutes after the end of the stress test.

| End point type | Secondary |
|---|---|

End point timeframe:

60 minutes before until 100 minutes after stress test, i.e.: -60 min, +15 min, +45 min, +100 min

| End point values | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 23 | | |
| Units: ng/l | | | | |
| median (full range (min-max)) | | | | |
| -60 min | 44.6 (10 to 108) | 37 (11 to 98.6) | | |
| +15 min | 35.4 (10 to 146) | 31 (10 to 88.4) | | |
| +45 min | 37.3 (10 to 105) | 32 (9.1 to 95.5) | | |
| +100 min | 29.8 (0 to 87.7) | 33 (10 to 104) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Norepinephrine

| End point title | Norepinephrine |
|---|---|

End point description:

The stress biomarker norepinephrine was measured before and after a stress test. The measurements started 60 minutes before stress test and were repeated until 100 minutes after the end of the stress test.

| End point type | Secondary |
|---|---|

End point timeframe:

60 minutes before until 100 minutes after stress test, i.e.: -60 min, +15 min, +45 min, +100 min

| End point values | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 30 | 23 | | |
| Units: ng/l | | | | |
| median (full range (min-max)) | | | | |
| -60 min | 484.5 (249 to 923) | 457 (195 to 797) | | |
| +15 min | 575.5 (299 to 1128) | 529 (279 to 1688) | | |
| +45 min | 458 (220 to 889) | 459 (223 to 858) | | |
| +100 min | 467 (269 to 938) | 372 (189 to 839) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma cortisol

| End point title | Plasma cortisol |
|---|---|

End point description:

The stress biomarker plasma cortisol was measured before and after a stress test. The measurements started 60 minutes before stress test and were repeated until 100 minutes after the end of the stress test.

| End point type | Secondary |
|---|---|

End point timeframe:

60 minutes before until 100 minutes after stress test, i.e.: -60 min, +15 min, +45 min, +100 min

| End point values | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 24 | | |
| Units: nmol/l | | | | |
| median (full range (min-max)) | | | | |
| -60 min | 365.9 (105.11 to 917.95) | 337.6 (125.51 to 836.49) | | |
| +15 min | 554.3 (72.19 to 971.2) | 544.3 (124.52 to 942.52) | | |
| +45 min | 466.8 (73.66 to 842.18) | 506.8 (121.6 to 815.16) | | |
| +100 min | 285.1 (83.99 to 735.4) | 285.1 (136.69 to 637.67) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change in Natural killer cells

| End point title | Change in Natural killer cells |
|---|---|

End point description:

The Natural Killer (NK) Cells as immune cells and stress biomarkers were measured before and after a stress test. The measurements started 60 minutes before stress test and were repeated until 100 minutes after the end of the stress test.

| End point type | Secondary |
|---|---|

End point timeframe:

60 minutes before until 100 minutes after stress test, i.e.: -60 min, +15 min, +45 min, +100 min

| End point values | Essen Neurexan group | Essen Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 15 | 12 | | |
| Units: % of lymphocytes | | | | |
| median (full range (min-max)) | | | | |
| -60 min | 11.8 (5.8 to 22.6) | 11.2 (5.6 to 16.5) | | |
| +15 min | 21.3 (9.8 to 28.1) | 17.7 (10.1 to 26.2) | | |
| +45 min | 11.6 (4.6 to 14.8) | 8.6 (4.3 to 12.7) | | |
| +100 min | 11.1 (6.1 to 18.2) | 7.8 (4 to 20.3) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Systolic blood presssure

| End point title | Systolic blood presssure |
|---|---|

End point description:

Systolic blood pressure was measured before and after a stress test by continuous cardiovascular recording. The measurements started 30 minutes before stress test and were repeated until 45 minutes after the end of the stress test.

| End point type | Secondary |
|---|---|

End point timeframe:

30 minutes before until 45 minutes after stress test, i.e.: -15 min, 0 min, +15 min, +45 min

| End point values | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 32 | | |
| Units: mmHg | | | | |
| median (full range (min-max)) | | | | |
| -15 min | 120.5 (86 to 175) | 123.5 (95 to 147) | | |
| 0 min | 131 (98 to 204) | 136.5 (96 to 171) | | |
| +15 min | 123 (92 to 161) | 128.5 (86 to 165) | | |
| +45 min | 121 (77 to 180) | 122 (91 to 160) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Diastolic blood pressure

| End point title | Diastolic blood pressure |
|---|---|

End point description:

Diastoblic blood pressure was measured before and after a stress test by continuous cardiovascular recording. The measurements started 30 minutes before stress test and were repeated until 45 minutes after the end of the stress test.

| End point type | Secondary |
|---|---|

End point timeframe:

30 minutes before until 45 minutes after stress test, i.e.: -15 min, 0 min, +15 min, +45 min

| End point values | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 32 | | |
| Units: mmHg | | | | |
| median (full range (min-max)) | | | | |
| -15 min | 78 (51 to 120) | 79 (56 to 103) | | |
| 0 min | 83.5 (59 to 138) | 88.5 (60 to 114) | | |
| +15 min | 81.5 (54 to 115) | 83 (54 to 109) | | |
| +45 min | 78 (40 to 124) | 81 (41 to 109) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Heart rate

| End point title | Heart rate |
|---|---|

End point description:

Heart rate was measured before and after a stress test by continuous cardiovascular recording. The measurements started 30 minutes before stress test and were repeated until 45 minutes after the end of the stress test.

| End point type | Secondary |
|---|---|

End point timeframe:

30 minutes before until 45 minutes after stress test, i.e.: -15 min, 0 min, +15 min, +45 min

| **End point values** | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 32 | | |
| Units: beats per minute | | | | |
| median (full range (min-max)) | | | | |
| -15 min | 67 (55 to 96) | 69 (49 to 98) | | |
| 0 min | 87 (67 to 135) | 83 (56 to 125) | | |
| +15 min | 68 (54 to 90) | 71 (44 to 93) | | |
| +45 min | 68 (56 to 96) | 72 (48 to 92) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Modified somatic SCL90

| End point title | Modified somatic SCL90 |
|---|---|

End point description:

The SCL90 has 90 items and covers dimensions like depression, somatization, obsessive-compulsive disorder, social insecurity, anxiety, phobic anxiety, aggression/hostility, paranoid ideation, psychoticism. A new instrument covering potential somatic stress consequences was used in this study, the modified somatic SCL90 that uses the SCL90 somatization items, but instead of a 7 day timeframe asking for "now" (current state). The corresponding items from SCL90 were: 1, 4, 12, 27, 40, 42, 48, 49, 52, 53, 56, 58 and the introductory question had to be: “How much do you currently suffer from...” ("Wie sehr leiden Sie momentan unter:").

| End point type | Secondary |
|---|---|

End point timeframe:

210 minutes before and 100 minutes after stress test, i.e: -210 min, +100 min

| **End point values** | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 32 | | |
| Units: score points | | | | |
| median (full range (min-max)) | | | | |
| -210 min | 0.042 (0 to 0.67) | 0.083 (0 to 1.08) | | |

| | | | | |
|---|---|---|---|---|
| +100 min | 0 (0 to 0.5) | 0 (0 to 0.33) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: State anxiety and stress perception measured by State-Trait

| End point title | State anxiety and stress perception measured by State-Trait |
|---|---|

End point description:

State anxiety and stress perception were measured by State-Trait Anxiety Inventory X1 before and after a stress test. The measurements took place 90 minutes before stress test and were repeated 15 and 100 minutes after the end of the stress test.

| End point type | Secondary |
|---|---|

End point timeframe:

90 minutes before stress test and 15 and 100 minutes after the end of the stress test, i.e.: -90 min, +15 min, +100 min

| **End point values** | Neurexan group | Natoural course group | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 | 32 | | |
| Units: score points | | | | |
| median (full range (min-max)) | | | | |
| -90 min | 32 (21 to 49) | 33 (22 to 43) | | |
| +15 min | 51 (33 to 73) | 56 (29 to 78) | | |
| +100 min | 32 (21 to 43) | 32 (20 to 52) | | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Randomization until individual study end, i.e.: i.e.: -180 min, -150 min, -120 min, -90 min, -60 min, -30min, -15 min, 0 min, +15 min, +30 min, +45 min, +60 min, +75 min, +100 min

Adverse event reporting additional description:

All adverse events that occurred after the participant has received at least one dose of the product under investigation (or same timepoint without intake for natural course) were to be collected and reported

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Neurexan group |

Reporting group description:

33 participants were randomized to Neurexan. One premature terminator could not be evaluated for primary efficacy, so 32 participants in the Neurexan group formed the full analysis Set for analysis of efficacy. All randomised subjects were included in the analysis of safety.

| | |
|---|---|
| Reporting group title | Natoural course group |

Reporting group description:

All of the 32 participants randomised to the Natural Course group formed the full analysis set for analysis of efficacy and safety.

| **Serious adverse events** | Neurexan group | Natoural course group | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 0 / 32 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| **Non-serious adverse events** | Neurexan group | Natoural course group | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 4 / 33 (12.12%) | 3 / 32 (9.38%) | |
| Investigations | | | |
| Alanin aminotransferase increased | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 32 (3.13%) | |
| occurrences (all) | 0 | 1 | |
| Aspartate aminotransferase increased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 32 (3.13%) | |
| occurrences (all) | 0 | 1 | |
| Injury, poisoning and procedural complications | | | |
| Procedural pain | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 1 / 32 (3.13%) | |
| occurrences (all) | 1 | 1 | |
| Procedural dizziness | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 32 (3.13%) | |
| occurrences (all) | 0 | 1 | |
| Procedural nausea | | | |
| subjects affected / exposed | 0 / 33 (0.00%) | 1 / 32 (3.13%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 32 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 32 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gastrointestinal disorders | | | |
| Dry mouth | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | 0 / 32 (0.00%) | |
| occurrences (all) | 1 | 0 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references


http://www.ncbi.nlm.nih.gov/pubmed/17615391

http://www.ncbi.nlm.nih.gov/pubmed/16952284

http://www.ncbi.nlm.nih.gov/pubmed/8255414

http://www.ncbi.nlm.nih.gov/pubmed/19837490

http://www.ncbi.nlm.nih.gov/pubmed/4303377

http://www.ncbi.nlm.nih.gov/pubmed/5535207

http://www.ncbi.nlm.nih.gov/pubmed/10600217

http://www.ncbi.nlm.nih.gov/pubmed/8598500

http://www.ncbi.nlm.nih.gov/pubmed/9491439