Clinical trial results:
Neuronal correlates of Neurexan® action in mildly to moderately stressed probands - a randomized, placebo-controlled, double-blind, cross-over trial of mode of action and response prediction by functional magnetic resonance imaging MRI

Summary

EudraCT number	2015-001802-32
Trial protocol	DE
Global end of trial date	03 December 2015

Results information

Result version number	v1 (current)
This version publication date	02 September 2022
First version publication date	02 September 2022

Trial information

Trial identification

Sponsor protocol code	C1501

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02602275
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biologische Heilmittel Heel GmbH
Sponsor organisation address	Dr.-Reckeweg-Straße 2-4, Baden-Baden, Germany, 76532
Public contact	Biologische Heilmittel Heel GmbH, Biologische Heilmittel Heel GmbH, +49 72215010, info@heel.com
Scientific contact	Biologische Heilmittel Heel GmbH, Biologische Heilmittel Heel GmbH, +49 72215010, 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	03 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 December 2015
Global end of trial reached?	Yes
Global end of trial date	03 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this clinical trial was to explore via functional MRI (fMRI) the effects of Neurexan® on the neuronal response in different brain regions while participants were either at rest or underwent different tasks in Verum compared to Placebo. The different tasks assessed by fMRI were an emotional task (Hariri) and a stress task (ScanStress) as the main interest was evaluating Neurexan's effect on the brain stress response.

Protection of trial subjects:

The trial was conducted in compliance with the protocol, the ethical principles of the Declaration of Helsinki, the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), and all applicable national laws and regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2015
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: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	40
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a single centre trial at the Clinical Affective Neuroimaging Laboratory (CANLAB), Magdeburg, Germany. Screening was restricted to the area of the site.

Pre-assignment

Screening details:

Screening was restricted to healthy males, aged 31 to 59 years, with mild to moderate chronic stress. Screening was stopped after inclusion of the anticipated 40 participants. One subject was withdrawn due to a 'cerebral finding' on Day 1 before the treatment with the investigational medication was started (no dose applied).

Period 1

Period 1 title	overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

This was a double-blind, randomised trial and all involved personnel on site, at the sponsor and the CRO were blinded during the trial. No emergency unblinding was necessary during the trial.

Arms

Are arms mutually exclusive?	No
Arm title	Neurexan

Arm description:

Participants received a single dose of three tablets Neurexan on one of two trial days (Day 1 or Day 2). The Neurexan "arm" describes the Neurexan condition of the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan - on the other day, the same participants received Placebo.

Arm type	Experimental
Investigational medicinal product name	Neurexan
Investigational medicinal product code	Nx4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Single sublingual administration of 3 tablets Neurexan

Arm title	Placebo

Arm description:

Participants received a single dose of three tablets Placebo on one of two trial days (Day 1 or Day 2). The Placebo "arm" describes the Placebo condition of the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan - on the other day, the same participants received Neurexan.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Single sublingual administration of 3 tablets Placebo

Number of subjects in period 1	Neurexan	Placebo
Started	39	39
Completed	39	39

Period 2	
Period 2 title	Baseline
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Neurexan - Placebo

Arm description:

Participants received a single dose of three tablets Neurexan on Day 1 and Placebo on Day 2 of the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.

Arm type	Experimental
Investigational medicinal product name	Neurexan
Investigational medicinal product code	Nx4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Single sublingual administration of 3 tablets Neurexan

Arm title	Placebo - Neurexan

Arm description:

Participants received a single dose of three tablets Placebo on Day 1 and Neurexan on Day 2 of the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.

Arm type	Experimental
Investigational medicinal product name	Neurexan
Investigational medicinal product code	Nx4
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Single sublingual administration of 3 tablets Neurexan

Investigational medicinal product name	Neurexan
Investigational medicinal product code	Nx4
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Sublingual use

Dosage and administration details:

Single sublingual administration of 3 tablets Neurexan

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: This was a crossover trial and the trial results were reported per condition (Verum vs Placebo) in an "overall trial" period as suggested in "Option 3" FAQ83, EudraCT & EU CTR Frequently asked questions. A second period (baseline) is given for reporting the baseline characteristics of the two sequences, Placebo first and Verum first.

Number of subjects in period 2[2]	Neurexan - Placebo	Placebo - Neurexan
Started	20	19
Completed	20	19

Notes:

[2] - 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: Out of 40 randomised subjects, 39 subjects were included into the safety, ITT and PP evaluation. One subject was withdrawn from trial before trial medication was started (no dose applied) and the subject was excluded from all analysis populations.

Baseline characteristics

Reporting groups	
Reporting group title	Neurexan - Placebo
Reporting group description:	
Participants received a single dose of three tablets Neurexan on Day 1 and Placebo on Day 2 of the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.	
Reporting group title	Placebo - Neurexan
Reporting group description:	
Participants received a single dose of three tablets Placebo on Day 1 and Neurexan on Day 2 of the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.	

Reporting group values	Neurexan - Placebo	Placebo - Neurexan	Total
Number of subjects	20	19	39
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	43.2	43.7	
standard deviation	± 10.0	± 9.6	-
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	20	19	39

End points

End points reporting groups

Reporting group title	Neurexan

Reporting group description:

Participants received a single dose of three tablets Neurexan on one of two trial days (Day 1 or Day 2). The Neurexan "arm" describes the Neurexan condition of the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan - on the other day, the same participants received Placebo.

Reporting group title	Placebo

Reporting group description:

Participants received a single dose of three tablets Placebo on one of two trial days (Day 1 or Day 2). The Placebo "arm" describes the Placebo condition of the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan - on the other day, the same participants received Neurexan.

Reporting group title	Neurexan - Placebo

Reporting group description:

Participants received a single dose of three tablets Neurexan on Day 1 and Placebo on Day 2 of the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.

Reporting group title	Placebo - Neurexan

Reporting group description:

Participants received a single dose of three tablets Placebo on Day 1 and Neurexan on Day 2 of the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.

Primary: Reduced amygdala responsiveness measured by negative face to form contrasts in the Hariri task after Verum versus Placebo condition

End point title	Reduced amygdala responsiveness measured by negative face to form contrasts in the Hariri task after Verum versus Placebo condition

End point description:

Effect of drug, driven by significantly smaller amygdala activations Blood Oxygenation Level Dependent (BOLD) response in the contrast (negative faces vs forms) in Neurexan compared to Placebo conditions. Significance level is 0.05, corrected for multiple comparisons in the search volume which is anatomically defined by the AAL (Automated Anatomical Labelling Atlas) coordinates.

End point type	Primary

End point timeframe:

Endpoint assessed about 1 hour post dose after a single dose of Neurexan or Placebo

End point values	Neurexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: Beta value				
arithmetic mean (standard deviation)	0.196 (± 0.045)	0.361 (± 0.040)		

Statistical analyses

Statistical analysis title	Paired T-Test

Statistical analysis description:

Paired t-test analysis for the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.

Comparison groups	Neurexan v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Paired t-test

Primary: Reduced functional connectivity density in amygdala after Verum versus Placebo condition during rest

End point title	Reduced functional connectivity density in amygdala after Verum versus Placebo condition during rest

End point description:

Interaction of time and drug, driven by significantly greater reductions of amygdala functional connectivity density (FCD) in Verum compared to Placebo conditions. Significance level was 0.05, corrected for multiple comparisons in the search volume which is anatomically defined by the AAL (Automated Anatomical Labelling Atlas) coordinates.

End point type	Primary

End point timeframe:

Endpoint assessed about 1 hour post dose after a single dose of Neurexan or Placebo

End point values	Neurexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35[1]	35[2]		
Units: FCD strength				
arithmetic mean (standard deviation)	0.0139 (± 0.1338)	-0.0073 (± 0.0855)		

Notes:

[1] - 3 excluded due to high micro-movement artefacts and 1 excluded due to data corruption.

[2] - 3 excluded due to high micro-movement artefacts and 1 excluded due to data corruption.

Statistical analyses

Statistical analysis title	Paired T-Test

Statistical analysis description:

Paired t-test analysis for the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.

Comparison groups	Neurexan v Placebo

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05
Method	Paired t-test

Primary: Reduced whole brain functional connectivity of amygdala after Verum versus Placebo condition during rest

End point title	Reduced whole brain functional connectivity of amygdala after Verum versus Placebo condition during rest

End point description:

Interaction of time and drug, driven by significantly greater changes of amygdala seeded connectivities in Verum compared to Placebo conditions. Significance level is 0.05, corrected for multiple comparisons in the whole brain.

End point type	Primary

End point timeframe:

Endpoint assessed about 1 hour post dose after a single dose of Neurexan or Placebo

End point values	Neurexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35[3]	35[4]		
Units: Binary connectivity coefficient				
arithmetic mean (standard deviation)	-0.0127 (± 0.0328)	0.0239 (± 0.0346)		

Notes:

[3] - 3 subjects excluded due to high micro-movement artefacts and 1 excluded due to data corruption

[4] - 3 subjects excluded due to high micro-movement artefacts and 1 excluded due to data corruption

Statistical analyses

Statistical analysis title	Paired T-Test

Statistical analysis description:

Paired t-test analysis for the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.

Comparison groups	Neurexan v Placebo
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Paired t-test

Notes:

[5] - Since we controlled for multiplicity due to multiple primary hypotheses by means of the principle of a priori ordered hypotheses and a preceding endpoint was not met, the outcome of this analysis was regarded as purely exploratory.

Primary: Reduced local resting state activity of amygdala after Verum versus Placebo condition

End point title	Reduced local resting state activity of amygdala after Verum versus Placebo condition

End point description:

Interaction of time and drug, driven by significantly greater reductions of amygdala ALFF in Verum compared to Placebo conditions. Significance level is 0.05, corrected for multiple comparisons in the search volume which is anatomically defined by the AAL (Automated Anatomical Labelling Atlas) coordinates.

End point type	Primary

End point timeframe:

Endpoint assessed about 1 hour post dose after a single dose of Neurexan or Placebo

End point values	Neurexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	21		
Units: fractional ALFF				
arithmetic mean (standard deviation)	-0.0120 (± 0.02534)	0.0007 (± 0.03590)		

Statistical analyses

Statistical analysis title	Paired T-Test

Statistical analysis description:

Paired t-test analysis for the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.

Comparison groups	Placebo v Neurexan
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.05 [6]
Method	Paired t-test

Notes:

[6] - Since we controlled for multiplicity due to multiple primary hypotheses by means of the principle of a priori ordered hypotheses and a preceding endpoint was not met, the outcome of this analysis was regarded as purely exploratory.

Primary: Reduced stress network activation during stress in Verum versus Placebo condition

End point title	Reduced stress network activation during stress in Verum versus Placebo condition

End point description:

Effect of drug, driven by significantly smaller activations in anterior cingulate cortex, medio-orbitofrontal cortex, hippocampus, amygdala, and hypothalamus in the contrast (hard vs easy) in Verum compared to Placebo conditions. Significance level is 0.05, corrected for multiple comparisons in the search volume which is anatomically defined by the AAL (Automated Anatomical Labelling Atlas) coordinates.

End point type	Primary

End point timeframe:

Endpoint assessed about 1.5 hours post dose after a single dose of Neurexan or Placebo

End point values	Neurexan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36[7]	36[8]		
Units: Beta Estimate				
arithmetic mean (standard deviation)	0.02 (± 0.14)	0.41 (± 0.14)		

Notes:

[7] - 3 excluded due to high micro-movement artefacts

[8] - 3 excluded due to high micro-movement artefacts

Statistical analyses

Statistical analysis title	Paired T-Test

Statistical analysis description:

Paired t-test analysis for the two-period, two-treatment crossover trial with 1:1 randomisation of the two treatment sequences Neurexan-Placebo and Placebo-Neurexan.

Comparison groups	Placebo v Neurexan
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05 [9]
Method	Paired t-test

Notes:

[9] - Since we controlled for multiplicity due to multiple primary hypotheses by means of the principle of a priori ordered hypotheses and a preceding endpoint was not met, the outcome of this analysis was regarded as purely exploratory.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Continuous recording of all adverse events on treatment days after randomisation and receipt of at least one dose of the IMP. Serious procedure-related adverse events were reported starting from the enrolment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Neurexan
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Neurexan	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Neurexan	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 39 (0.00%)	0 / 39 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events occurred during the trial.

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limited to male participants with mild to moderate chronic stress.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32123197

http://www.ncbi.nlm.nih.gov/pubmed/35438535

http://www.ncbi.nlm.nih.gov/pubmed/34912250

http://www.ncbi.nlm.nih.gov/pubmed/35213077

http://www.ncbi.nlm.nih.gov/pubmed/34729551