2. Synopsis

Name of company: Biologische Heilmittel Heel GmbH	Summary table referring to part of the dossier,	(For National Authority use only)
Name of finished product: Neurexan®	Volume: Page:	
Name of active ingredient: Homeopathic preparation containing *Passiflora incarnata, Avena sativa, Coffea arabica, Zincum isovalerianicum*, lactose monohydrate and magnesium stearate.		

Title:	Efficacy profile of Neurexan® in an experimental acute stress setting – an explorative open-label study in healthy probands
Principal investigators:	[redacted]
Study centres:	2 centres in Marburg and Essen, a list of study centres is provided in Appendix 16.1.4.
Dates of study:	First proband in: 12 Oct 2012 Last visit of last proband: 04 Apr 2013
Clinical phase:	I/II
Publications:	No publication on this study available at the time of this report. The study design was presented at the international congress PROGRESS IN OUR UNDERSTANDING OF THE PSYCHOBIOLOGICAL AND NEUROBIOLOGICAL MECHANISMS OF THE PLACEBO AND NOCEBO RESPONSES 23 to 25 Jan 2013 in Tübingen (Henze et al., 2013).
Objectives:	To evaluate the efficacy profile of **acutely dosed** Neurexan in a randomised study using the Trier Social Stress Test (TSST), an experimental acute stress test protocol. *Primary objective:* The primary objective was 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. *Secondary objectives* of the study were stress-sensitive psychological and physiological measures in response to acute stress: • stress-related biomarkers such as plasma and saliva cortisol, α-amylase, adrenocorticotropic hormone (ACTH), catecholamines, natural killer (NK) cells • parameters of autonomous nervous system (ANS) such as blood pressure (BP), heart rate and heart rate variability (HRV) • state anxiety and stress perception measured by State-Trait Anxiety Inventory (STAI) • psychological questionnaire (modified somatic Symptom Checklist 90 [SCL90])

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Methodology:	Prospective two-arm two-site trial with an explorative randomised, open-label study design
Number of subjects planned and analysed:	Planned size: 70 probands (35 for each treatment group) were planned to be randomised to achieve 60 evaluable probands (30 for each treatment group). Randomised: 65 probands (33 Neurexan vs. 32 Natural Course) Safety Set: 65 probands (33 Neurexan vs. 32 Natural Course) Full Analysis Set: 64 probands (32 Neurexan vs. 32 Natural Course) Per-Protocol (PP) Set: 64 probands (32 Neurexan vs. 32 Natural Course)
Diagnosis and main criteria for inclusion:	For inclusion in the study, probands had to comply with all of the following criteria: • Provide written informed consent • Healthy male or female • Age between 31 to 59 years • Fluent in German language • Ability to understand the explanations and instructions given by the study physician
Dosage and administration:	
Test product	Neurexan: *Passiflora incarnata* dilution (Dil.) D2 (0.6 mg/tablet), *Avena sativa* Dil. D2 (0.6 mg/tablet), *Coffea arabica* Dil. D12 (0.6 mg/tablet), *Zincum isovalerianicum* Dil. D4 (0.6 mg/tablet), lactose monohydrate, magnesium stearate. Bulk number: 9519
Reference therapy	Natural course: no tablet intake or other therapeutic intervention.
Duration of treatment:	At baseline, probands took a total of 6 tablets of either Neurexan or had no intake (natural course) over a period of 2.5 hours.

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Criteria for evaluation:	**Primary endpoints:** • Area under the curve (AUC) of VAS tension values from Timepoint T1 (V3, -210 min) until Timepoint T15 (V3, +100 min). • AUC of VAS nervousness values from T1 until T15. For each of the two AUCs an analysis of covariance (ANCOVA) model including gender and site as qualitative factors and the respective VAS value (i.e. tension or nervousness) at time point T1 (-210 min) as a covariate was analysed to test for treatment differences **Secondary endpoints:** • Changes in tension and nervousness VAS at all time points after time point T1 (-210 min) • Changes in plasma and saliva cortisol and α-amylase, ACTH, catecholamines norepinephrine (NE) and epinephrine (E) • Changes in NK cells (subgroup) • Changes in BP, heart rate and HRV • State anxiety and stress perception measured by STAI-X1 • Incidence of adverse events (AEs) All parameters were descriptively summarised by treatment and assessment time. The AEs and vital signs were summarised by treatment group.
Statistical methods:	All statistical analyses in this study were of exploratory nature. The summaries of the efficacy parameters, the statistical analyses of the primary efficacy variable, and the statistical analyses of the secondary efficacy variables were performed on the Full Analysis Set. These summaries and analyses were supported by corresponding summaries and exploratory statistical analyses performed on the PP Set. Missing values for all secondary efficacy parameters were imputed by the last observation carried forward (LOCF) approach, unless specified otherwise in the Statistical Analysis Plan (SAP). All statistical tests were supported by presenting estimates and 95% confidence intervals for the respective treatment effects and differences between the treatment groups. These estimates and confidence intervals were based on the respective statistical models used for the analysis. All parameters were descriptively summarised by treatment and assessment time. The AEs and vital signs were summarised by treatment group. The descriptive analyses of the tension and nervousness VAS values were performed for males and females separately.

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Summary and Conclusions (trade marks not shown in results part):

Baseline and demography:

Treatment groups were similar with regard to demographic and baseline data including PSS and STAI-X2 while baseline mean stress levels were higher in the Natural Course group than the Neurexan group for the VAS scores as well as TICS-SCSS, TICS and SCL90. There were no major protocol violations in this study.

Efficacy Results:

Primary efficacy parameter

AUC of tension and nervousness VAS

The VAS AUCs were lower in the Neurexan group than in the Natural Course group. The median AUC of tension VAS was 3089.4 in the Neurexan group and 3253.4 in the Natural Course group while the median AUC of nervousness VAS was 2377.3 in the Neurexan group and 3426.8 in the Natural Course group.
The t-test based on ANCOVA with factors treatment, gender, site and T1 value as covariate showed no significant influence of gender while the baseline VAS value at T1 had a significant influence on the VAS AUCs, but was based on the assumption of normal distribution.
Since the final analysis revealed considerable doubt about the implicit normality assumption of the two sets of AUC data, the following non-parametric analyses were carried out in addition as sensitivity analyses:
Wilcoxon tests for treatment differences of VAS tension and nervousness for both AUC and baseline-corrected AUC, i.e. AUC – 310*Baseline AUC.
Van Elteren tests for treatment differences of VAS tension and nervousness for both AUC and baseline-corrected AUC, stratified by gender and site.
Neither test revealed new major findings, however, this indicated the need further in-depth analysis of data ex-post.

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Secondary Efficacy Variables:

Changes in tension and nervousness VAS at all time points after time point T1 (-210 min)

The course of VAS values over time clearly reflected the experimental acute stress setting. All median VAS values for tension and nervousness were below 16 over the entire course of the study except for the time point T10 (15 minutes after start of acute stress exposure) where VAS median values were 24.5 for Neurexan and 36.5 for Natural Course for tension and 28.5 for Neurexan and 39.0 for Natural Course for nervousness.

Changes in plasma and saliva cortisol and α-amylase, ACTH, catecholamines, norepinephrine (NE) and epinephrine (E) and in NK cells (subgroup)

At T10 (+15 min), all median values of parameters (alpha-amylase activity, saliva cortisol, ACTH, plasma cortisol and noradrenaline [norepinephrine], NK cell numbers) increased compared to first measurement at T6 (-60 min). All parameters decreased afterwards until T15 (+100 min) again.

Changes in BP, heart rate and heart rate variability (HRV)

The vital signs changes corresponded well with the experimental stress setting. At T10 (+15 min), systolic BP, diastolic BP and heart rate increased remarkably compared to baseline (T-8) and decreased afterwards again towards the baseline (T8) values. The heart rate variability was similar between the treatment groups.

Psychological questionnaire (modified somatic SCL90)

The modified somatic SCL90 average scores showed similar median changes from T1 (-210 min) to T15 (+100 min) at baseline visit in both treatment groups. The modified SCL90 median average score changed from 0.042 at T1 (-210 min) to 0.000 at T15 (+100 min) in the Neurexan group and from 0.083 at T1 (-210 min) to 0.000 at T15 (+100 min) in the Natural Course group.

State anxiety and stress perception measured by STAI-X1

The overall STAI-X1 median sum score changed from 32.0 at T5 (-90 min) to 53.0 at T10 (+15 min) and decreased again to 32.0 at T15 (+100 min) with no relevant differences between the treatment groups.

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Safety Results:

A total of 10 AEs was reported in 7 (10.8%) probands, thereof 5 AEs in 4 (12.1%) probands in the Neurexan group and 5 AEs in 3 (9.4%) probands in the Natural Course group. Most AEs could be expected for this specific type of stress procedure; these were 3 AEs of dizziness, 2 AEs of procedural pain, and single AEs of dry mouth, procedural nausea, headache, increased alanine aminotransferase (ALAT) and increased aspartate aminotransferase (ASAT). All AEs were non-serious and of mild or moderate intensity and were reported as fully resolved/recovered.
All AEs in the Neurexan group were mild. According to the investigator all AEs had no or an unlikely causality to the study medication while in 8 of 10 AEs at least a possible relationship to study procedures was assessed. No AE led to premature discontinuation from the study.

According to the company internal assessment (Heel) a possible relatedness to the study medication occurred only in one single case. This single case is considered not to be of any safety relevance.

In summary, from both, investigator and company internal assessment, treatment groups were similar with regard to frequency, relationship, distribution, intensity, premature termination or seriousness of AEs.

There were no relevant differences between the treatment groups at baseline for any haematology and biochemistry parameter. Two AEs in proband 1-114 in the Natural Course group were moderate increases of ALAT with 53 U/L at T0 (-240 min) and 64 U/L at T15 (+100 min) and of ASAT with 218 U/L at T15 (+100 min), but as the proband had no therapeutic intervention at all, this was not regarded as clinically relevant. In summary, there were no noteworthy laboratory abnormalities in this study.

Conclusions:

In conclusion, the changes in primary and secondary efficacy parameters corresponded well with the experimental acute stress setting. However, the results are linked to the specific study design (sample size, dosing scheme, experimental setting, explorative pilot study). Also, the final analysis revealed considerable doubt about the implicit normality assumption of the two sets of AUC data. All these findings show the need of a further investigation (ex-post analyses). Taking all observations together, Neurexan was as safe as no therapeutic intervention and very well tolerated.

Date of the report: 03 December 2013