


2. Synopsis

<u>Name of company:</u> Biologische Heilmittel Heel GmbH	<u>Summary table referring to part of the dossier,</u>	<u>(For National Authority use only)</u>
<u>Name of finished product:</u> Neurexan	<u>Volume:</u> <u>Page:</u>	
<u>Name of active ingredient:</u> Homeopathic preparation containing <i>Passiflora incarnata</i> , <i>Avena sativa</i> , <i>Coffea arabica</i> , <i>Zincum isovalerianicum</i> , lactose monohydrate and magnesium stearate.		
<u>Title:</u>	Efficacy profile of Neurexan® in an experimental acute stress setting – an explorative double-blind study in healthy probands	
<u>Principal investigators:</u>		
<u>Study centres:</u>	2 centres in Marburg and Essen, a list of study centres is provided in Appendix 16.1.4.	
<u>Dates of study:</u>	First proband in: 18 Oct 2012 Last visit of last proband: 02 Apr 2013	
<u>Clinical phase:</u>	I/II	
<u>Publications:</u>	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, Germany (Henze et al., 2013).	
<u>Objectives:</u>	<p>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.</p> <p><u>Primary objective:</u> 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 Placebo. The test method for this study is the TSST protocol.</p> <p><u>Secondary objectives</u> of the study were stress-sensitive psychological and physiological measures in response to acute stress:</p> <ul style="list-style-type: none"> • stress-related biomarkers such as plasma and saliva cortisol, α-amylase, adrenocorticotrophic 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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<u>Methodology:</u>	Prospective two-arm two-site trial with an explorative randomised, double-blind study design	
<u>Number of subjects planned and analysed:</u>	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: 66 probands (34 Neurexan vs. 32 Placebo) Safety Set: 66 probands (34 Neurexan vs. 32 Placebo) Full Analysis Set : 64 probands (34 Neurexan vs. 30 Placebo) Per-Protocol (PP) Set: 64 probands (34 Neurexan vs. 30 Placebo)	
<u>Diagnosis and main criteria for inclusion:</u>	For inclusion in the study, probands had to comply with all of the following criteria: <ul style="list-style-type: none"> • 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 	
<u>Dosage and administration:</u>		
<u>Test product</u>	Neurexan: <i>Passiflora incarnata</i> dilution (Dil.) D2 (0.6 mg/tablet), <i>Avena sativa</i> Dil. D2 (0.6 mg/tablet), <i>Coffea arabica</i> Dil. D12 (0.6 mg/tablet), <i>Zincum isovalerianicum</i> Dil. D4 (0.6 mg/tablet), lactose monohydrate, magnesium stearate. Bulk number: 9519.	
<u>Reference therapy</u>	Placebo: Lactose monohydrate, magnesium stearate. Bulk number: 49151	
<u>Duration of treatment:</u>	At baseline, probands took a total of 6 tablets of either Neurexan or matching Placebo over a period of 2.5 hours.	

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Criteria for evaluation:	Primary endpoints: <ul style="list-style-type: none"> 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. <p>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</p> Secondary endpoints: <ul style="list-style-type: none"> 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) <p>All parameters were descriptively summarised by treatment and assessment time. The AEs and vital signs were summarised by treatment group.</p>	
Statistical methods:	<p>All statistical analyses in this study were of exploratory nature.</p> <p>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.</p> <p>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).</p> <p>All statistical tests were supported by presenting estimates and 95% confidence intervals (CIs) for the respective treatment effects and differences between the treatment groups. These estimates and CIs were based on the respective statistical models used for the analysis.</p> <p>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.</p>	

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Summary and Conclusions: Baseline and demography: Treatment groups were similar with regard to demographic and baseline data including TICS, TICS-SCSS, SCL90 score, PSS and STAI-X2. There were no major protocol violations in this study. Efficacy Results: Primary Efficacy Variable AUC of tension and nervousness VAS Treatment groups were similar with regard to tension and nervousness measured by VAS AUC. The median AUC of tension VAS was 3335.7 in the Neurexan group and 3360.3 in the Placebo group while the median AUC of nervousness VAS was 3147.4 in the Neurexan group and 3022.5 in the Placebo group. The t-test based on ANCOVA with factors treatment, gender, site and T1 value as covariate showed no significant influence of gender and site 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. $AUC - 310 \times \text{Baseline AUC}$. 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) <p>The course of VAS values over time clearly reflected the experimental acute stress setting. All median VAS values for tension and nervousness were equal or below 15.0 over the entire course of the study except for the time point T10 (15 minutes after start of acute stress exposure) where median VAS values were 39.0 for Neurexan and 47.0 for Placebo for tension and 40.5 for Neurexan and 38.0 for Placebo for nervousness.</p> Changes in plasma and saliva cortisol and α-amylase, ACTH, catecholamines, norepinephrine (NE) and epinephrine (E) and NK cells (subgroup) <p>The changes of alpha-amylase activity and cortisol saliva concentrations and blood samples corresponded well with the experimental stress setting. 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) with exception of adrenaline (epinephrine) that did not show a clear trend. All parameters decreased afterwards until T15 (+100 min) again.</p> Changes in BP, heart rate and heart rate variability (HRV) <p>The vital signs changes corresponded well with the experimental stress setting. At T10 (+15 min), systolic BP and heart rate increased remarkably compared to baseline (T8) and decreased afterwards again towards the baseline (T8) values. The heart rate variability was similar between the treatment groups.</p> Psychological questionnaire (modified somatic SCL90) <p>The modified somatic SCL90 average scores showed no median changes from T1 (-210 min) to T15 (+100 min) at baseline visit in both treatment groups. The modified SCL90 median average score was 0.0 at T1 (-210 min) and at T15 (+100 min) in both groups.</p> State anxiety and stress perception measured by STAI-X1 <p>The STAI-X1 value changes corresponded well with the experimental stress setting. The overall STAI-X1 median sum score changed from 31.0 at T5 (-90 min) to 53.5 at T10 (+15 min) and decreased again to 32.5 at T15 (+100 min) with no relevant differences between the treatment groups.</p>		

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Safety Results: <p>A total of 15 AEs was reported in 7 (10.6%) probands, thereof 6 AEs in 4 (11.8%) probands in the Neurexan group and 9 AEs in 3 (9.4%) probands in the Placebo group. These were 4 AEs of dizziness, 3 AEs of decreased blood pressure, 2 AEs of headache and hyperhidrosis each, and single AEs of fatigue, feeling cold, tremor (in legs) and nausea.</p> <p>All AEs were non-serious and of mild intensity and were reported as fully resolved/recovered. According to the investigator one case of fatigue in the Placebo group was assessed with a possible relationship to study drug and no relationship to study procedure, all other AEs had no or an unlikely causality to the study medication while at least a possible relationship to study procedures was reported. One AE in proband 2-110 in the Placebo group with a definite relationship to study procedure led to premature discontinuation from the study.</p> <p>According to the company internal assessment (Heel) no relatedness to the intake of the study medication (verum) occurred for all of the reported events.</p> <p>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.</p> <p>There were no relevant differences between the treatment groups at baseline for any haematology and biochemistry parameter. No AE related to laboratory abnormal values was reported in this study. In summary, there were no noteworthy laboratory abnormalities in this study.</p>		
Conclusions: <p>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, and 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 Placebo and very well tolerated.</p> <p>Date of the report: 03 December 2013</p>		