Synopsis

Name of Sponsor:
Weleda AG, Dychweg 14, 4144 Arlesheim, Switzerland

Name of Finished Product:
Neurodoron®

Names of active ingredients:
Gold D10
Kalium phosphoricum D6
Ferrum-Quartz D2

Title of Study:
Efficacy and safety of Neurodoron® in patients with nervous exhaustion – a randomized, double-blind, placebo-controlled clinical trial
according to approved study protocol version 2.0 dating from 18 July 2011; there were no amendments

Investigator:
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Study centre:
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Publication (reference):
None.

Studied period (years): 1 year

- Date of first enrolment: 01 September 2011
- Date of last completed: 04 September 2012
- The study was neither interrupted nor discontinued nor previously terminated.

Phase of development:
IV

Objectives:
Primary objective was demonstration of efficacy of Neurodoron® in patients with nervous exhaustion by means of reduction of symptoms, reduction of subjectively perceived stress and improvement of the subjectively perceived general health status.

Secondary objectives investigated the influence of Neurodoron® on the extent of tedium, on the time until symptoms of exhaustion abated as well as the proportion of patients who responded to the treatment. The safety of treatment was investigated on the basis of type and severity of adverse events as well as safety laboratory parameters.

Methodology:

The clinical trial was conducted in Germany as mono-centre, randomized, double-blind, placebo-controlled study with parallel group comparison. All patients fulfilling the selection criteria have been treated for six weeks with either Neurodoron® or placebo in the dosage 3x1 tablets/day. After two weeks of medicamentous treatment a control visit was carried out by the doctor, after additional four weeks a final visit. Before treatment started and at each visit patients assessed 12 characteristic symptoms of exhaustion (irritability, restlessness, nervousness, listlessness, depressive mood, mood swings, anxiety states, troubles to concentrate/lack of concentration, headache, sleep disorders, digestive disorders, muscular pain/ tensions) from 0 (not present) to 3 (severe), their subjectively perceived stress (Perceived Stress Questionnaire, PSQ, according to Fliege et al.), their general health status (Short Form Health Survey, SF-36), the extent of tedium (Tedium Measure according to Pines/Aronson/Kafry) and gave particulars regarding the subjectively perceived onset of effect as well as adverse events. Before start of treatment and after 6 weeks blood samples for the safety laboratory were taken.

Number of patients (planned and analysed):

Treatment group	**Planned***	**Screened**	**Randomized**	**Intention-to-Treat (ITT)-Population**	**Per Protocol (pP)- Population**	**Safety-Population**
Neurodoron®	91	no treatment	78	77	65	77
Placebo	91		78	77	66	77
Total	**182**	**204**	**156**	**154**	**131**	**154**

* The planned number of patients included an estimated rate of 20% screening failures. For confirmatory analysis 146 evaluable patients were planned.

Diagnosis and main criteria for inclusion:

The diagnosis was made according to the ICD-10-criteria for “nervous exhaustion” (WHO, 1993). A persistent and distressing feeling of exhaustion after minor mental effort or a persistent and distressing feeling of fatigue and bodily weakness after minor physical effort had to be existent for at least 3 months. At the same time at least one of the characteristic symptoms dizziness, headache, muscular aches and pains, sleep disturbance, inability to relax or irritability had to be present. The patients had to be at least 18 years of age and their informed consent had to be obtained according to the legal regulations. A possible organic cause for the disease had to be diagnostically excluded before start of treatment.

Test product, dose and mode of administration, batch number:

Neurodoron® tablets, 3x1 tablets daily, oral, batch-no.: 273-11

Duration of treatment:

6 weeks

Reference therapy, dose and mode of administration, batch number:

Placebo tablets, 3x1 tablets daily, oral, batch-no.: 1-11

Criteria for evaluation:

Efficacy:

Primary efficacy variables:

1. Type and severity of characteristic symptoms relating to nervous exhaustion, measured by a symptom-sumscore consisting of the summed assessments for the 12 characteristic symptoms of exhaustion
2. Subjectively perceived stress, measured by means of Perceived Stress Questionnaire (PSQ) according to Fliege et al.
3. General health status, measured by Short Form Health Survey (SF-36)

Secondary efficacy variables:

1. Tedium Measure according to Pines/Aronson/Kafry
2. Time until subjectively perceived onset of treatment effect (abating of symptoms of exhaustion)
3. Proportion of patients with improvement ≥50% (measured by means of symptom-sumscore)

Safety:

1. Number, type and severity of adverse and serious adverse events
2. Type and frequency of clinically relevant laboratory value changes

Statistical methods:

All demographic and baseline data were descriptively analysed. The homogeneity of treatment groups was tested.

For confirmatory analysis, the three primary efficacy variables were tested in hierarchical order. All analyses were carried out using Student's t-test for two independent samples on the same one-sided alpha-level of 0,025 (equivalent to 0,05 two-sided).

The secondary efficacy variables were exploratively analysed. For this purpose, group compparisons were carried out using statistical tests; the results of these analyses are indicative yet not confirmatory.

The primary statistical analysis was carried out as intention-to-treat (ITT) analysis, i. e. all patients who had administered at least one dose of the study medication were included.

Summary of results and conclusion:

Out of 204 screened patients, 154 were randomised.

The data of all 154 patients were included in the ITT-analysis.

In both treatment groups, patients had a mean age of approximately 53 years and more than 70% were female. With respect to baseline data there were no relevant differences.

The following table summarises the efficacy results.

Efficacy results (ITT-analysis, after 6 weeks of treatment):

Efficacy variables	Treatment group		Difference [95% CI]	p-value; stat. test
	Placebo N = 77	Neurodoron® N = 77		
Primary efficacy variables				
Symptom-sumscore Mean, (SD)	10.88 (6.0)	10.55 (5.7)	0.3 [-1.5; 2.2]	0.7275; t-test
PSQ Mean, (SD)	39.96 (18.3)	41.93 (18.0)	-2.0 [-7.8; 3.9]	0.5048; t-test
SF-36				
Physical subscale Mean, (SD)	47.33 (9.0)	46.91 (9.0)	0.4 [-2.5; 3.3]	0.7733; t-test
Mental subscale Mean, (SD)	44.36 (12.0)	43.07 (12.0)	1.3 [-2.6; 5.1]	0.5102; t-test
Secondary efficacy variables				
Tedium measure Mean, (SD)	2.92 (1.0)	3.07 (0.8)	-0.1 [-0.4; 0.1]	0.3181; t-test
Time until onset of effect Median in days, (range)	39 (29-47)	37 (27-44)	-	0.4571; log-rank test
Number of patients with improvement of symptom-sumscore ≥50% (%)	16 (20.8)	19 (24.7)	-	0.5539; Fisher's exact test

SD: Standard deviation; CI: Confidence interval

For none of the investigated efficacy variables, an advantage in favour of Neurodoron® could be demonstrated.

Safety results:

The safety-population included all 154 randomised patients. 12 adverse events (AE) were assessed as causal. 6 of the AE (in 5 patients) occured under placebo, 6 AE (in 6 patients) under Neurodoron®. Mainly the gastrointestinal tract was affected. There were no signs for abnormalities in the blood tests. Consequently, the safety of Neurodoron® can be assessed as markedly good.

Conclusion:

The controlled clinical trial had the objective to investigate the specific drug effect of Neurodoron®. None of the investigated efficacy variables showed an advantage for the Neurodoron® group, in this respect a specific drug effect regarding the observed parameters could not be demonstrated under the controlled study conditions.

Thereby the effects observed in a previously conducted non-interventional study (NIS) could not be confirmed. As the results of nervous exhaustion are manifold, individual therapy with several simultaneous measures is common practice. The individual therapeutic approach considers the patient within his entire life situation. The positive results of the previously conducted NIS reflect common treatment practice insofar more adequately. However, the design of a NIS does not permit evaluation of the specific drug effect of Neurodoron® as too many drugs and measures are applied simultaneously and a control group is missing. The controlled clinical trial showed that administration of Neurodoron® as sole measure in nervous

exhaustion is not sufficient under the specific conditions of randomisation and blinding.

The result of the NIS that positive effects under treatment with Neurodoron® as part of a therapeutic concept can be observed remains still valid.

Date of report: 31 July 2013