SYNOPSIS

Name and address of the sponsor: WALA Heilmittel GmbH Dorfstr. 1 73085 Bad Boll/Eckwälden	**Reference to the dossier:** not applicable	***(For use by the Higher Federal Authority)***
Project Management: Institute of Social Medicine, Epidemiology and Health Economics Berlin		
Name of the approved medicinal product: Disci/Rhus toxicodendron comp.		
Active ingredients: Aconitum napellus e tubere ferm 33c Dil. D4, 0.1g Argentum metallicum Dil. D18 aquos., 0.1g Arnica montana e planta tota ferm 33c Dil. D18, 0.1g Disci intervertebrales bovis (cervicales, thoracici et lumbales) Gl Dil. D6, 0.1g Formica rufa ex animale toto Gl Dil. D5, 0.1g Gelsemium sempervirens e rhizoma ferm 35b Dil. D2, 0.1g Granit Dil. D8, 0.1g Leontopodium alpinum e planta tota ferm 36 Dil. D2, 0.1g Mandragora officinarum e radice ferm 34d Dil. D4, 0.1g Phyllostachys e nodo ferm 35c Dil. D4, 0.1g Toxicodendron quercifolium e foliis ferm 33d Dil. D4, 0.1g		
Title of the clinical trial: Prospective, randomized, controlled, multicentre, partly double blind study to compare Disci/Rhus toxicodendron comp., placebo and waiting list in patients with chronic low back pain.		
Investigators: Dr. Jürgen Bachmann (consent given) Orthopaedics August-Bebel-Straße 8-10 45525 Hattlingen Kliniken Essen Mitte Knappschaftskrankenhaus, Innere V Prof. Dr. med. Gustav Dobos (consent given) Am Deimelsberg 34a 45276 Essen Dr. Christine Dühn (consent given) Specialist in orthopaedics Pestalozzistr. 10 03226 Vetschau Practice in Dobra (consent not available) Practice in Bergisch-Gladbach (consent not available) Practice in Cottbus (consent not available) Practice in Hof (consent not available) 2 practices in Berlin (consent not available) Clinic in Jena (consent not available) Clinic in Berlin (consent not available)		
Centres of the clinical trial: 11 centres – see under Investigators.		

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Phyllostachys e nodo ferm 35c Dil. D4, 0.1g
Toxicodendron quercifolium e foliis ferm 33d Dil. D4, 0.1g

Publications: Pach D, Brinkhaus B, Roll S, Wegscheider K, Icke K, et al. (2011) Efficacy of Injections with Disci/Rhus Toxicodendron Compositum for Chronic Low Back Pain – A Randomized Placebo-Controlled Trial. PLoS ONE 6(11): e26166. doi:10.1371/journal.pone.0026166.

Duration of the clinical trial: First patient in: August 23, 2007 Last patient out: July 23, 2008 (Intervention group)	**Phase of the clinical trial:** Phase IV

Objective and parameters:
The primary objective was to investigate whether Disci/Rhus toxicodendron comp. is more effective than no treatment (waiting list group) or more effective than a placebo in the treatment of chronic low back pain.

1) Average pain relative to the last 7 days (measured on the basis of a visual analogue scale (0-100 mm) after 8 weeks (primary target parameter))
2) Back function (Hanover Functional Ability Questionnaire – Back FFbH-R after 8 and 26 weeks
3) Average pain relative to the last 7 days (visual analogue scale (0-100 mm) after 26 weeks
4) Number of days with acute medication needs in weeks 1-4, 5-8 and 1-8 (patient diary)
5) Number of days of incapacity for work in the case of gainfully employed study participants in weeks 5-8 (patient diary)
6) Number of visits to the doctor due to backache in weeks 5-8 (patient diary)
7) Health-related quality of life (SF-36) after 8 and 26 weeks
8) Emotional pain assessment (Pain Sensation Scale, PSS) after 8 and 26 weeks
9) Assessment of the impairment in everyday life (Pain Disability Index) after 8 and 26 weeks
10) Influence of the patient's expectations on the average pain in relation to the last 7 days (measured using a visual analogue scale (0-100 mm) after 8 and 26 weeks).
11) Influence of the doctor's expectations on the average pain in relation to the last 7 days (measured using a visual analogue scale (0-100 mm) after 8 and 26 weeks).
12) Influence of the number of therapy sessions on the average pain relative to the last 7 days (measured using a visual analogue scale (0-100 mm)) after 8 and 26 weeks

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Phyllostachys e nodo ferm 35c Dil. D4, 0.1g
Toxicodendron quercifolium e foliis ferm 33d Dil. D4, 0.1g

13) 33% responder rates for the average pain after 8 and 26 weeks relative to the last 7 days (visual analogue scale 0-100 mm)

Methodology:
The study was conducted as a prospective, randomised, controlled, partly double-blind (verum vs. placebo injection), partly open (comparison with waiting list group) multicentre study (11 centres). The study was designed to compare the efficacy of the 10 ml dose of Disci/Rhus toxicodendron comp. vs. the untreated control group (waiting list group) or vs. 10 ml placebo injection. The primary outcome measure (the average pain over the last 7 days measured on the VAS 0-100 mm) was determined after 8 weeks of treatment. The total observation period per patient was 26 weeks, during the course of which further secondary target parameters were collected.

Number of trial participants:
In accordance with the planned number of participants, 150 subjects were included and evaluated according to an intention-to-treat analysis.

Inclusion criteria:

1) Male and/or female study participants aged between 30 and 75
2) Willingness of the study participant to follow the instructions of the investigator, i.e. to comply with the study conditions.
3) Presence of the clinical diagnosis "chronic low back pain" (chronic local or pseudoradicular pain in the area of the lumbar spine due to e.g. an underlying degenerative disease with exclusion of the diagnoses referred to below).
4) Pain in the lumbar spine for at least 12 months (= chronic low back pain), and the standard therapeutic measures must have been exhausted
5) Average value of the pain intensity relative to the last 7 days ≥ 40 mm on a visual analogue scale of 0-100 mm
6) In the last 4 weeks, only drug therapy of the lumbar spine complaints (as-needed treatment with peripherally acting analgesics, non-steroidal anti-inflammatory drugs and muscle relaxants).

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Toxicodendron quercifolium e foliis ferm 33d Dil. D4, 0.1g

7) Willingness to use sufficient/effective contraception in women of child-bearing age. Contraceptive measures are considered effective if the failure rate is <1%/year, e.g. oral hormonal contraception with combination preparations, implants, intrauterine device, diaphragm device, cervical valve or sexual abstinence.
8) Written informed consent form

Exclusion criteria:
1) Previous or current treatment with Disci medicinal products
2) As-needed treatment of the pain with analgesics other than those that act peripherally and non-steroidal anti-inflammatory drugs (NSAIDs).
3) Regular (>1/week) use of painkillers due to other illnesses
4) Protrusion or prolapse of one or more intervertebral disc(s) with neurological symptoms
5) Previous spinal operations
6) Suspected infectious spondylopathy
7) Spinal complaints due to malignant and inflammatory disease
8) Organic causes of the symptoms such as Bekhterev's disease, Reiter's disease or Behcet's disease
9) Congenital deformities of the spine with the exception of slight lordosis, kyphosis or scoliosis.
10) Suspected osteoporosis with compression fracture of one or more vertebral bodies
11) Suspected spinal stenosis
12) Spondylolysis or spondylolisthesis
13) Physiotherapy planned in the last 4 weeks before the start of the study or during the study
14) Beginning of a new therapy for the treatment of the lumbar spine pain in the past 4 weeks.
15) Already planned new therapy (including operations) for the treatment of lumbar spine pain during the study period
16) Complementary medicine therapy (e.g. acupuncture, homeopathy, phytotherapy, neural therapy) planned in the last 4 weeks before the start of the study or during the study
17) Patients who, for linguistic, intellectual or other reasons, cannot be expected to be able to understand the importance of the clinical trial and demonstrate the necessary compliance for this.
18) Patients with alcohol, medication and/or drug addiction

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19) Simultaneous participation in other clinical trials. The last participation in a clinical trial must be at least three months ago.
20) The presence of a serious and/or acute or chronic organic or mental illness with severe impairment of the patient's general condition which makes it impossible for him or her to take part regularly in a clinical trial.
21) Patients with coagulation disorders or those taking anti-coagulant medications
22) Pregnant patients (presence of a positive pregnancy test during the inclusion examination) and breast-feeding women.
23) Patients with a current pension application
24) Study participants who are entrusted with the planning and performance of the study
25) Known hypersensitivity to any of the ingredients

Investigational Medicinal Product, Dosage and Administration, Batch Number
Disci/Rhus toxicodendron comp. (Batch no. 710710):
The patients participated in 12 therapy sessions: 8 in the first 4 weeks (2x/week at intervals of at least one day without therapy) and 4 in the last 4 weeks (1x/week at intervals of at least three days without therapy).
During each therapy session, 10 ml (1 ampoule) of intervention solution was applied (verum group: Disci/Rhus toxicodendron comp., placebo group: isotonic solution). The application is carried out subcutaneously using 0.4 mm needles and 10 ml syringes in 5-10 partial quantities at several sites in the pain area of the lumbar spine. The patients in the waiting list group did not receive any intervention.

Length of the therapy:
The total observation time per patient was 26 weeks. The duration of the study for the patients in the verum and placebo group consisted of the treatment phase (8 weeks) and the follow-up phase (18 weeks). The duration of the study included a 26-week waiting period for patients in the waiting list group.

Comparator Product, Dosage and Administration, Batch Number
Isotonic solution (batch no. 710710):
The patients participated in 12 therapy sessions: 8 in the first 4 weeks (2x/week at intervals of at least one day without therapy) and 4 in the last 4 weeks (1x/week at intervals of at least three days without therapy).
During each therapy session, 10 ml (1 ampoule) of intervention solution was applied (verum group:

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Formica rufa ex animale toto Gl Dil. D5, 0.1g
Gelsemium sempervirens e rhizoma ferm 35b Dil. D2, 0.1g
Granit Dil. D8, 0.1g
Leontopodium alpinum e planta tota ferm 36 Dil. D2, 0.1g
Mandragora officinarum e radice ferm 34d Dil. D4, 0.1g
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Disci/Rhus toxicodendron comp., placebo group: isotonic solution).
The application is carried out subcutaneously using 0.4 mm needles and 10 ml syringes in 5-10 partial quantities at several sites in the pain area of the lumbar spine. The patients in the waiting list group did not receive any intervention.

Evaluation criteria:
Efficacy: Average pain relative to the last 7 days (measured on the basis of a visual analogue scale (0-100 mm))[5] after 8 weeks.

Safety: The continual collection and evaluation of adverse events (AEs) and serious adverse events (SAEs) was carried out.

Statistical analyses:
1) Multi-level model with the two levels of patient and practice (adjusted for the baseline value at the patient level), without the replacement of missing values (Model 1)
2) Sensitivity analysis with maximum likelihood-based imputation of missing values (regression method with the variables of the baseline VAS (visual analogue scale), age and gender).
3) Sensitivity analysis with the imputation of missing values by means of worst-case procedures.
4) Analysis of the secondary target parameters with Model 1 or any other appropriate Generalised Linear Model (GLM).
5) Further covariates (with and without interaction) in Model 1 or the GLM
6) Repeated measurement multilevel models

Summary – Conclusion

Study population: 150 patients (36% men, 57.6±10.7 (mean value (MV) ± standard deviation (SD) years old); 64% women; 56.3±11.2 years old; duration of complaints 14.5±12.3 years) were included between August 2007 and June 2008. For 8 patients there were no follow-up values available.

Results on efficacy: Compared to a group without therapy, the lumbar spine pain of patients who were treated with the anthroposophical medicine Disci/Rhus toxicodendron comp. improved to an extent which was both statistically significant and clinically relevant during the therapy. However, there was no significant difference compared to the placebo group.

For the primary endpoint (Visual Analogue Scale (VAS), 0-100 mm after 8 weeks), the following

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VAS values were found for the comparison between the verum group and the waiting list group: Verum: 37.02±4.38 (MV±standard error (SE)), 97.5% confidence interval (CI) [25.27;48.77]) and waiting list: 52.97±4.30 [41.75;64.19], p=0.001). The comparison of the verum versus placebo resulted in the following VAS values: Verum: 37.02±4.38 [25.27;48,77] and placebo: 41.83±4.59 [30.09;53.58], p=0.350). The results for the secondary outcome measures support the results for the primary outcome measure.

The secondary target parameters, as well as the per-protocol analysis and further sensitivity analyses confirm the primary result.

After 26 weeks there was only a trend in favour of the Disci/Rhus toxicodendron comp. group compared to the waiting list group.

Safety results: Of the 99 patients in the two intervention groups, a total of 71 patients (verum group: 37 patients, placebo group: 34 patients) reported at least one Adverse Event. Reported Adverse Events for at least two or more study participants mainly comprise haematomas in the injection area (verum group: 8 patients (15.7%) versus placebo group: 5 patients (10.4%)), common cold (9 (17.6%) vs. 5 (10.4%)) and various types of pain (22 (11.2%) vs. 25 (12.0%). No statistically significant differences were found between the verum and placebo groups.

Adverse events in the verum group with mild intensity were reported by 17 patients, with moderate intensity by 19 patients and with severe intensity by 10 patients.
In the placebo group, 21 patients reported Adverse Events of mild intensity, 18 patients Adverse Events of moderate intensity and 12 patients Adverse Events of severe intensity. The following Adverse Events were assessed by the treating physician to be probably or definitely associated with the therapy. Verum group: Heavy legs and increase in the discomfort (n=1), sciatica (n=1), itching (n=1), sweating (n=1), haematoma in the injection area (n=8), lumbar spine pain (n=2). Placebo group: Neck pain (n=1), haematoma in the injection area, buttocks and back (n=5), skin changes on the hand (n=1), paraesthesias in the injection area (n=2), redness in the injection area (n=1), pain in the back (n=2).

There were no serious adverse events with a causal relationship to the study medication.

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Results for the secondary target parameters: The difference in the pain intensity as shown by the VAS for the comparison between the verum group and the waiting list group, which was still statistically significant after 8 weeks, did not reach any statistical significance after 26 weeks. In the placebo group there was only a trend after 26 weeks towards lower pain intensity as measured by the VAS than in the waiting list group. During the therapy period, the patients in the verum group needed their acute medication on fewer than half of the days compared to the waiting list group. In the placebo group, the patients in the therapy phase needed their acute medication on a statistically lower number of days than the patients in the waiting list group. The SF-36 as a measuring instrument for recording the health-related quality of life showed no statistically significant differences for either the physical or the mental sum scale in the verum group compared to the waiting list group after 8 weeks and after 26 weeks. Only for the sub-scales of Physical Pain and Psychological Well-Being were statistically significant differences determined after 8 weeks. However, these were each expressed in the opposite directions and did not therefore show a uniform result. In SF-36 as a measuring instrument for recording the health-related quality of life, there were statistically significant differences between the placebo group and the waiting list group for the physical sum scale in favour of the placebo group after both 8 weeks and 26 weeks. For the mental sum scale, a trend in favour of the waiting list group only became evident after 8 weeks. For the sub-scales of Physical Pain and Vitality it was also only possible after eight weeks to determine trends in favour of the placebo group in each case (physical pain). After 26 weeks there was also a trend in favour of the placebo group for the General Health Perception sub-scale. For all other sub-scales of SF-36 it was not possible to determine any other group differences.
Both the Pain Sensation Scale (PSS) and the Hanover Functional Ability Questionnaire - Back - (FFbH-R) showed no differences either between the verum and waiting list group or between the placebo and waiting list group for the time points 8 and 26 weeks. The Pain Disability Index (PDI: low values better) showed a difference between the verum group and waiting list group after 26 weeks that was statistically significant. The comparison of the verum group and the placebo group showed no statistically significant differences for the secondary outcome measures investigated.
Between the placebo group and the waiting list group, the Pain Disability Index (PDI: low scores better) showed a trend towards a difference after 8 weeks. The low probability of occurrence of

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days of incapacity for work did not permit any model calculation. It was therefore not possible to determine any differences between the groups. The visits to the doctor for back pain also occurred so infrequently that there was no model calculation. The chance of achieving a 33% improvement (33% responder rate: improvement of at least 33% starting from the baseline value) was more than 5 times greater for patients in the verum group compared to patients in the waiting list group after 8 weeks. Compared to the placebo group, there was no advantage for the verum group. After 26 weeks there were no significant differences in the chances between the groups. The results of the Visual Analogue Scale after 8 weeks, taking into account various possible further influencing variables (patient expectations, doctor and number of therapy sessions), show that even the inclusion of further covariates would not significantly change the results of the primary analysis. In the interaction test it becomes clear that the effect of the intervention was not significantly dependent on the patient characteristics (covariates) that were presented.
The comparison of the placebo group and the waiting list group also showed a statistically significant difference for the primary outcome measure. Patients in the placebo group reported a statistically significant lower level of pain after 8 weeks than patients in the waiting list group.
Conclusion: The therapeutic use of the medication Disci/Rhus toxicodendron comp. has been shown to be safe and harmless in the present study. Disci/Rhus toxicodendron comp. was superior to no treatment. However, the injection of Disci/Rhus toxicodendron comp. was not more effective in patients with chronic low back pain than the injection of a placebo.

Change to the Trial Protocol

Trial protocol version 02 of March 19, 2007, approval on March 28, 2007

Changes compared to the trial protocol version 01_December 19, 2006:

Synopsis point 6: Target patient population: Inclusion criteria point 4	Pain in the lumbar spine for at least 12 months, and the standard therapeutic measures must have been exhausted - was inserted
Synopsis point 6: Target patient population: Inclusion criteria point 7	Contraceptive measures are considered effective if the failure rate is <1%/year, e.g. oral hormonal contraception with combination preparations, Implants, intrauterine device, diaphragm device,

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	cervical valve or sexual abstinence – was inserted.
Synopsis point 6: Target patient population: Exclusion criteria point 21	“serious” - was deleted
Synopsis point 8: Test duration:	Sentence: "Subsequently, patients in the waiting list group are offered Disci/Rhus toxicodendron comp. treatment outside the study evaluation" - was deleted.
Trial protocol 4.2: Inclusion criteria point 4	Pain in the lumbar spine for at least 12 months, and the standard therapeutic measures must have been exhausted - was inserted
Trial protocol 4.2: Inclusion criteria point 7.	Contraceptive measures are considered effective if the failure rate is <1%/year, e.g. oral hormonal contraception with combination preparations, implants, intrauterine device, diaphragm device, cervical valve or sexual abstinence - was inserted.
Trial protocol 4.3: Exclusion criteria point 21:	“serious” - was deleted
Date of the Synopsis: December 18, 2009	