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# Treatment of anxiety, tension and restlessness states with Kava special extract WS® 1490 in general practice: A randomized placebo-controlled double-blind multicenter trial

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## Summary

**The efficacy and tolerability of 150 mg/d Kava special extract WS® 1490 were investigated in a randomized, placebo-controlled, double-blind multicenter study in patients suffering from neurotic anxiety (DSM-III-R diagnoses 300.02, 300.22, 300.23, 300.29, or 309.24). 141 adult, male and female out-patients received 3 × 1 capsule of 50 mg/d WS® 1490 or placebo for four weeks, followed by two weeks of observation without study-specific treatment.**
**During randomized treatment the total score of the Anxiety Status Inventory (ASI) observer rating scale showed more pronounced decreases in the WS® 1490 group than in the placebo group. Although a treatment group comparison of the post-treatment ASI scores was not significant ($p > 0.05$), an exploratory analysis of variance across the differences between treatment end and baseline, with center as a second factor, showed superiority of the herbal extract over placebo ($p < 0.01$, two-sided). 73% of the patients treated with WS® 1490 exhibited ASI score decreases >5 points versus baseline, compared to 56% for placebo. Significant advantages for WS® 1490 were also evident in a structured well-being self-rating scale (Bf-S) and the Clinical Global Impressions (CGI), while the Erlangen Anxiety, Tension and Aggression Scale (EAAS) and the Brief Test of Personality Structure (KEPS) showed only minor treatment group differences.**
**Although the results show consistent advantages for WS® 1490 over placebo in several psychiatric scales and indicate significant improvements in the patients' general well-being, the differences versus placebo were not as large as in previous trials which employed 300 mg/d of the same extract. WS® 1490 was well tolerated, with no influence on liver function tests and only one trivial adverse event (tiredness) attributable to the study drug.**

**Key words:** anxiety, clinical trial, efficacy, Kava, WS® 1490

## Introduction

Generalized anxiety disorder (GAD) is among the most common psychiatric diseases, with a lifetime prevalence of at least 5% in the general population and twice as high in women aged 40 or above (Wittchen and Hoyer, 2001). In the U.S.A., the 1994 National Comorbidity Survey showed a one-year prevalence of anxiety disorders of 17% and a lifetime prevalence approaching 25% (Kessler et al. 1994). Although anxiety disorders are thus among the most common psychiatric diseases in primary care (Hidalgo and Davidson, 2001), a

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recent Australian mental health survey suggests that more than half of the affected patients do not consult a healthcare professional for assistance (Andrews and Carter, 2001).

Traditionally pharmacological treatment of acute anxiety disorders has predominantly involved the administration of benzodiazepines. However, these drugs are known to cause disturbing side effects like addiction and withdrawal symptoms (e.g. Davidson, 2001; Lader, 1999). This may be one of the reasons why many patients are reluctant to take synthetic anxiolytic drugs, or do not consult a physician for help at all. Under these circumstances herbal drugs, which are mainly marketed as dietary supplements in the U.S.A., are often perceived as a safer or more natural alternative by patients and doctors alike (Cauffield and Forbes, 1999; Vincent and Furnham, 1996).

In case of anxiety disorder, the most widely used herbal drugs are based on extracts from the rhizome of the Kava plant *(Piper methysticum)* (e.g. Fugh-Berman and Cott, 1999). Such extracts have been used traditionally by peoples of the South Seas Islands because of their relaxant and hypnotic properties. To date, scientific research on the botanical and pharmacological properties of the herb has mainly been conducted in Germany (and hence many of the relevant publications are in German). Researchers have identified several pharmacologically active Kava pyrones, which have a primarily anxiolytic effect (e.g. Hänsel and Woelk, 1994; Hoelzl et al. 1994). In addition, Kava root extracts were also found to have muscle-relaxant, analgesic, anticonvulsant and neuroprotective properties (e.g. Backhauss and Krieglstein, 1992; Schmitz et al. 1995; Walden et al. 1997). These effects have been linked to a modulation of the GABAA binding site (Boonen and Haberlein, 1998; Jussofie et al. 1994), an inhibition of MAO-B (Uebelhack et al. 1998), an activation of the mesolimbic dopaminergic neurons and changes in the activity of 5-HT neurons (Baum et al. 1998) as well at to a modulation of serotonin-1A receptor activity (Walden et al. 1997) caused by the various constituents of the extract.

WS® 1490[a] is a special monoextract from the dried root of the Kava plant which is standardized to 70% Kava lactones and contains 30% of ancillary substances to promote absorption. It is licensed in Germany for the treatment of anxiety, tension and restlessness states. The efficacy and tolerability of WS® 1490 was evaluated in several placebo and reference controlled studies. In a review of seven double-blind, randomized, placebo-controlled trials with Kava extract monopreparations in patients suffering from anxiety disorders, Pittler and Ernst (2000) determined that the anxiolytic efficacy of the herbal extracts was superior to placebo in all of the primary publications. Three of these trials (Kinzler et al. 1991; Volz and Kieser, 1997; Warnecke, 1991), all of which used the special extract WS® 1490, used the Hamilton Anxiety Scale (HAM-A – Hamilton, 1976) total score reduction as the primary outcome measure for treatment efficacy and were thus entered into a meta-analysis, which resulted in a weight mean difference of 9.69 points (95% confidence interval: 3.54; 15.83) in favor of Kava extract. In another trial reported by Woelk and colleagues (1993), the authors did not find clinically relevant differences in efficacy between WS® 1490 300 mg/d, oxazepam 15 mg/d and bromazepam 9 mg/d. Malsch and Kieser (2001) studied patients changing over to WS® 1490 300 mg/d from a benzodiazepine treatment regimen and found that the herbal extract was not only superior to placebo, but the patients also exhibited significant improvements over benzodiazepine pre-treatment. Unlike benzodiazepines, tolerance effects, addiction or withdrawal symptoms have not been reported in pharmacological and clinical studies conducted with WS® 1490 to date.

In the three trials summarized by Pittler and Ernst (2000), WS® 1490 was administered at a daily dose of 300 mg (100 mg t.i.d.). This corresponds as well to the dosage preferred by many practitioners. According to the dosing recommendations in the monograph published on Kava root extract in the German Federal Legal Gazette (Bundesgesundheitsamt, 1990), however, a daily dose of 150 mg may be sufficient to produce an adequate anxiolytic effect. Although previous trials with WS® 1490 indicated that 300 mg/d is well tolerated and safe, achieving an appropriate anxiolytic effect with half of the dose is appealing since from the point of view of the risk-benefit assessment it is always preferable to achieve one's therapeutic aims with the lowest effective dose. We therefore investigated the efficacy and tolerability of 150 mg (50 mg t.i.d.) WS® 1490 in patients with anxiety, tension and restlessness states.

## Methods

### Ethical conduct of the trial

The present study was carried out in compliance with the Declaration of Helsinki, the EU recommendations of Good Clinical Practice (GCP) as well as national regulatory and legal requirements. Before the start of the study, the trial protocol was examined and approved by an independent ethics committee. Patients

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were informed about aims and procedures of the trial and gave their written informed consent before study entry.

### Subjects

The trial was conducted in male and female, adult outpatients who suffered from states of anxiety, tension and/or erethism (diagnosis according to DSM-III-R: agoraphobia [300.22], specific phobia [300.29], social phobia [300.23], generalized anxiety disorder [300.02], or adjustment disorder with anxiety [309.24]) and had a total score exceeding 18 points on the Hamilton Anxiety Scale (HAM-A). In order to exclude patients with inadequate capacity to complete the self-rating scales, a minimum of 13 points was required in the Multiple Choice Vocabulary Test (MWT-B – Lehrl, 1989) as well. Exclusion criteria were serious physical or psychiatric disorders (particularly those interfering with treatment with cerebrally active substances), suicidal tendencies, major depression, organic and schizophrenic psychoses, personality disorders; incapacity to complete the self-assessment scales, lack of cooperation, drug or alcohol abuse; acute intoxication by sedative drugs or alcohol; myasthenia gravis, cerebral ataxia or sleep apnea; arterial hypotension (systolic/diastolic blood pressure below 90/60 mm Hg); severe renal, hepatic, pulmonary, cardiovascular or neoplastic diseases; pregnancy and lactation. Concomitant medication with central nervous activity, e.g. psychostimulants, neuroleptics, antidepressants or tranquilizers, was not allowed during trial participation. Necessary cardiovascular drugs with possible central nervous effects were permitted if treatment had already started at least three months before study inclusion.

### Study design

The investigation was conducted as a prospective, double-blind, randomized, placebo-controlled, multicenter, parallel-group trial. The schedule of the investigational procedures is summarized in Table 1. After giving their informed consent to trial participation in writing, the patients underwent a comprehensive physical and psychiatric examination and were assessed for compliance with the inclusion and exclusion criteria.

Following a run-in period of seven days without study-specific medication, the participants underwent a baseline examination during which they were randomized to four weeks of double-blind treatment with 3 × 50 mg/day WS® 1490 or placebo. The random code was generated by a validated computer program, using a block size of 10 and a ratio of 1:1 between the two treatments. Each study center received only complete random blocks, and the patients were to be assigned to the lowest unused random number available at the center in chronological order of their randomization. The study medication was available in capsules containing either 50 mg of dry extract WS® 1490 (drug-extract ratio 11–20:1; extraction agent: acetonic water) standardized to 35 mg Kava lactones, or placebo. Both drugs were identical in all aspects of their appearance. During randomized treatment, study visits were conducted after one, two and four weeks. The double-blind phase was followed by two weeks of follow-up without study-specific treatment.

Compliance control was performed by counting the remaining medication and asking the patients about their drug intake. Correctness of the documentation and compliance with the protocol was assured by regular monitoring visits according to GCP recommendations.

**Table 1.** Investigational schedule.

| Investigations | Screening examinationa (1 week before start of treatment) | Base-line | After 1 week of treatment | After 2 weeks of treatment | End of treatment (after 4 weeks of treatment) | Follow-up (2 weeks after end of treatment) |
|---|---|---|---|---|---|---|
| Inclusion and exclusion criteria | X | | | | | |
| ASI | | X | X | X | X | X |
| EAAS | | X | X | X | X | X |
| Bf-S | | X | X | X | X | X |
| KEPS | | X | X | X | X | X |
| CGI | | X | X | X | X | X |
| Blood pressure, heart rate | | X | X | X | X | X |
| Laboratory parameters | | X | | | X | |
| Adverse events | | | X | X | X | X |

### Outcome measures

The primary outcome measure for treatment efficacy was the average total score of the Anxiety Status Inventory (ASI – Zung, 1971) at the end of randomized treatment (week 4). The ASI is an observer rating scale for the evaluation of anxiety as a symptom of various psychiatric disorders. The ratings have to be performed on the basis of the investigator's clinical observations, the patient's history, and a standardized, structured interview. The scale has 20 items which relate to affective (items 1–5 and 20) and somatic (items 6–19) manifestations of anxiety. Each symptom is rated on a four-point scale ranging from 1 (absent) to 4 (severe). While the HAM-A was chosen for establishing the patients' eligibility for the trial in order to maintain comparability with other studies, the ASI was given preference as the primary outcome measure because the efficacy of WS® 1490 with regard to HAM-A improvement had been demonstrated previously (Kinzler et al. 1991; Volz and Kieser, 1997; Warnecke, 1991) and it was intended to confirm these results by applying a different validated anxiety scale.

Secondary efficacy measures were the average intraindividual ASI total score change between baseline and treatment end, the Erlangen Anxiety, Tension and Aggression Scale (EAAS) – a self-rating scale for measuring situational anxiety and tension (Galster and Spörl, 1979), the 'Befindlichkeitsskala' (Bf-S) well-being self-rating scale (von Zerssen, 1976) with 28 pairs of contrasting adjectives to assess the current degree of impairment of subjective well-being, the Brief Test of Personality Structure (KEPS) – a self-rating scale representing personality structure in terms of subscores for neuroticism, extraversion, control and dominance (Weidenhammer and Burkhard, 1987), and the Clinical Global Impressions (CGI – National Institute of Mental Health, 1976). To assure consistency of results of the psychiatric ratings, the investigators were familiarized with the application of the diagnostic criteria and rating scales by an experienced rater during an investigator meeting and during a detailed study initiation visit.

Safety and tolerability of the investigational products were assessed by documenting any adverse events at each visit during and after randomized treatment, as well as by safety laboratory examinations (hematological status, erythrocyte sedimentation rate, ASAT, ALAT, γ-GT, sodium, potassium, glucose, triglycerides, cholesterol, creatinine, uric acid, TSH).

### Biometry

All randomized patients were included into the efficacy and safety analysis (for efficacy outcome measures, the last observation was carried forward in patients terminating treatment prematurely). The ASI post-treatment total scores were tested for treatment group differences with the Mann-Whitney U-Test and a type I error of $\alpha = 0.05$ (one-sided). In an additional descriptive analysis, the intraindividual ASI total score differences between baseline and week 4 of randomized treatment were tested for treatment group differences by means of a two-factor analysis of variance based on ranks, into which center was entered as a second factor to account for center differences. The other efficacy measures were evaluated using the methods of descriptive data analysis. SAS, version 6.4, was used for the statistical calculations.

Under the assumption of a stochastic superiority of WS® 1490 over placebo of 0.65 (i.e. for any randomly selected patient treated with WS® 1490, the probability to exhibit a better treatment response than a randomly selected patient treated with placebo was expected to be at least 65%) and a type I error of $\alpha = 0.05$ (one-sided), a sample size of $2 \times 75$ patients was required in order to have a power of at least 90% to reject the null hypothesis by means of a U-test.

## Results

### Patient characteristics

The study was conducted in 17 general practices in Germany. In total 141 patients were recruited, 71 of whom were randomized to WS® 1490 and 70 were assigned to placebo. Fig. 1 shows the disposition of patients and the number withdrawn prematurely. All randomized patients were evaluable according to intention-to-treat.

The patients' mean age was 48.8 (23–70) years in the WS® 1490 group and 48.2 (18–69) years in the placebo group. Seventy-four percent of the study participants (105 of 141) were female, with no relevant differences between the ratio of male and female patients within the two treatment groups.

With mean total scores (± SD) of 25.6 ± 5.5 points for WS® 1490 and 25.8 ± 6.6 points for placebo the average pre-treatment severity of the disorder according to the HAM-A was comparable in both study groups. The mean MWT-B scores also showed no relevant treatment group differences (27.0 ± 6.7 points versus 27.1 ± 4.9 points for WS® 1490 and placebo, respectively). In the differential diagnosis of the anxiety disorders, agoraphobic symptoms were observed in more than 40% of the patients in both treatment groups, followed by social phobias, specific phobias and generalized anxiety disorders (each in roughly 20% of the patients in both groups). According to their anamnesis, 55% of the patients felt unable to cope with their everyday lives, and about 38% were burdened with an actual or perceived loss of high subjective importance. Ac-

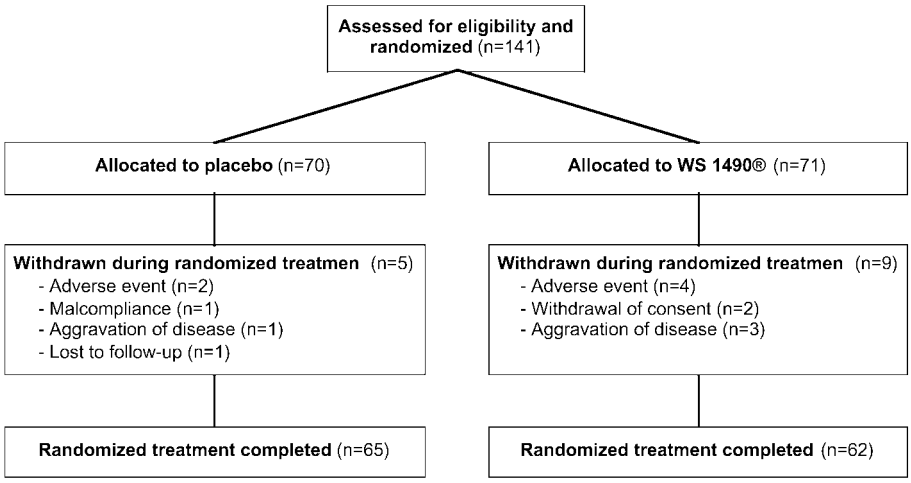


**Fig. 1.** Disposition of patients.

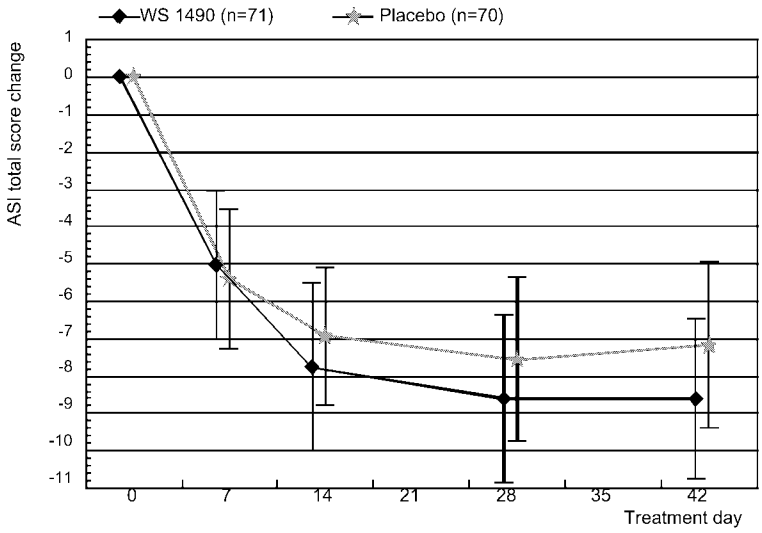


**Fig. 2.** ASI total score – change from baseline (means and 95% confidence intervals; last observation carried forward).

cording to the information given by the patients, the calculated mean duration of the anxiety disorder was 26 ± 73 months in the WS® 1490 group and 33 ± 80 months in the placebo group.

The data show that the two study groups were essentially comparable with respect to their baseline characteristics.

### Efficacy

Fig. 2 shows the time course of the ASI total score change versus baseline. The average severity of anxiety in both study groups decreased monotonically during randomized treatment. While the time course in the placebo group tended to level off after one week, the patients in the WS® 1490 group showed another substantial score decrease during the second week. Between baseline (day 0) and the end of randomized treatment (day 28) the average decrease in the ASI total score was 8.6 ± 9.1 points for WS® 1490 and 7.2 ± 9.5 points for placebo (mean ± SD; last observation carried forward). Based only on those patients who completed randomized treatment as scheduled, the ASI total score changes were 9.8 ± 8.6 and 7.9 ± 9.4 points for WS® 1490 and placebo, respectively. In the medication-free period during weeks 5 and 6 the average ASI total score was unchanged under WS® 1490 while the placebo group exhibited a slight aggravation.

Without baseline correction, the ASI total score means (with 95% confidence interval) at treatment end were 39.0 (36.6; 41.3) points for WS® 1490 and 40.6 (38.3; 43.0) points for placebo. The U-test for the difference between the treatment groups was not significant ($p > 0.05$). In the analysis of variance based on

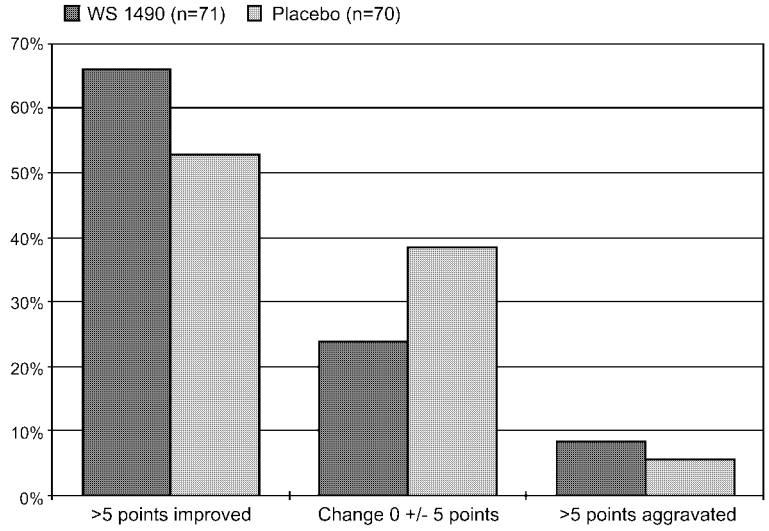


**Fig. 3.** Percentage of patients with and without improvement in ASI total score (last observation carried forward).

**Table 2.** Liver function tests (means ± SD).

| | WS® 1490 | | Placebo | |
|---|---|---|---|---|
| | pre-treatment (n = 70) | post-treatment (n = 65) | pre-treatment (n = 70) | post-treatment (n = 66) |
| GOT (U/l) | 10.6 ± 3.9 | 10.7 ± 3.7 | 11.3 ± 4.4 | 11.3 ± 6.0 |
| GPT (U/l) | 12.9 ± 8.8 | 12.0 ± 4.8 | 13.1 ± 5.0 | 12.1 ± 4.4 |
| γ-GT (U/l) | 16.4 ± 11.0 | 14.9 ± 6.4 | 15.7 ± 9.1 | 14.5 ± 7.7 |
| Alkaline phosphatase (U/l) | 110.2 ± 35.5 | 110.1 ± 34.3 | 109.8 ± 29.6 | 111.2 ± 29.3 |

ranks, the treatment group difference referring to the change versus baseline at week 4 was associated with a two-sided p-value < 0.001 in favor of WS® 1490. The analysis also revealed a large center effect (p < 0.001), but a negligible treatment by center interaction (p = 0.96).

With 66.2% for WS® 1490 and 53.9% for placebo, the percentage of patients whose ASI total score improved by more than 5 points during randomized treatment was by more than 12% larger in the group receiving the herbal extract (Fig. 3). Compared to WS® 1490, a larger percentage of patients in the placebo group showed only small score changes versus baseline, while four patients in each group exhibited a relevant aggravation of symptoms.

According to the investigators' ratings in the CGI 42% of the patients in the WS® 1490 group and 32% in the placebo group were much or very much improved at treatment end (full analysis set, last observation carried forward) This treatment group difference in favor of WS® 1490 is also reflected in the patients' self-rating of their general well-being according to the Bf-S in which the median (inter-quartile range) of the patients treated with the herbal extract decreased from 30 (20; 40) to 16 (8; 31) points, compared to a decrease from 32 (22; 40) to 22.5 (13; 36) points for placebo. This corresponds to a decrease of the median by 14 and 9.5 points for WS® 1490 and placebo respectively. The EAAS and the KEPS also reflected the over-all improvements in the patients' anxiety and psychic condition, but there were only marginal advantages in favor of WS® 1490.

### Tolerability

Of the 141 patients included in the study, 14 (9 in the WS® 1490 group and 5 in the placebo group) were withdrawn prematurely (cf. Fig. 1). In 6 of these patients (4 and 2 respectively) premature termination occurred in the context of adverse events all of which were assessed to be unrelated to the investigational treatment. In four patients (3 and 1) treatment was stopped because of symptom aggravation necessitating a change in anxiolytic medication. The examination of

the premature study terminators' data gave no indication of any adverse drug reactions (ADR).

Three additional adverse events during randomized treatment had no influence on the affected patients' study participation. One patient in the placebo group developed a ganglion on her left wrist and another patient reported sneezing attacks. In the WS® 1490 group one patient complained about increased tiredness with probable relationship to the investigational treatment. Neither physical examination nor vital signs assessment indicated any adverse effects. The same applied to the results of the safety laboratory examination (liver function tests in particular – cf. Table 2) where no systematic or individual changes towards abnormal values were observed.

## Discussion

Previous trials demonstrating the efficacy of Kava extract preparations in patients suffering from neurotic anxiety have predominantly employed drug dosages of 210 or 300 mg/d (Pittler and Ernst, 2000) which, in studies with WS® 1490 (Kinzler et al. 1991; Malsch and Kieser, 2001; Volz and Kieser, 1997; Warnecke, 1991), corresponds to approximately 150 to 210 mg Kava lactones. In this trial we investigated whether 150 mg/d WS® 1490 (corresponding to 105 mg/d Kava lactones), a dosage that is encountered quite frequently in clinical practice, are appropriate to bring about a sufficient anxiolytic effect.

Although superiority of the herbal extract could not be demonstrated in the confirmatory test based on the ASI total scores at treatment end (and thus not accounting for the baseline values), WS® 1490 was descriptively more effective than placebo in reducing neurotic anxiety as assessed by the investigators by means of the ASI as shown in the analysis of variance based on change versus baseline. The onset of the effect versus placebo was observed during the second week of double-blind treatment, after which the difference between the groups was retained until the end of the double-blind period. It was interesting to observe that while the anxiety ratings of the patients in the WS® 1490 group did not change after discontinuation of the herbal extract, the patients randomized to placebo exhibited slightly increasing anxiety scores after treatment was withdrawn.

A comparison of the change in the ASI total score during double-blind treatment determined for all patients (last observation carried forward) and in 'study completers' only shows a larger advantage for WS® 1490 in the latter group (ratio of means: 1.13 versus 1.36 in favor of WS® 1490). This is consistent with the fact that the number of patients withdrawn prematurely was nine for WS® 1490 and five for placebo, so that a larger percentage of patients in the WS® 1490 group terminated treatment before a satisfactory anxiolytic effect was achieved.

An important finding is that the beneficial effect of WS® 1490 was not only observed in the investigators' ratings, but was also reflected in the patients' self-assessment. Beyond the changes in the anxiety ratings this applied particularly to the patients' perception of their over-all well-being as measured by the Bf-S. These findings indicate that the study participants treated with WS® 1490 derived a considerable advantage from the investigational treatment, with a beneficial influence on their general condition.

Although previously published trials investigating the efficacy of WS® 1490 employed the HAM-A to obtain the investigator's rating of severity of anxiety, a comparison with the results of the ASI in our trial may be achieved by determining the ratio between the average change versus baseline in the WS® 1490 group and in the placebo group (Table 4 –- the trial by Malsch and Kieser, 2001 is not included here since they studied only patients changing over to WS® 1490 from benzodiazepine pre-treatment).

The table shows that that the advantage of WS® 1490 over placebo in our trial was in the range of Volz and Kieser (1997) whose results were, however, obtained in a long-term trial with a treatment phase of 25 weeks. The two trials with double-blind treatment phases not

**Table 3.** Mean change in investigator's rating of severity of anxiety during double-blind treatment, treatment duration and mean HAM-A baseline total score for WS® 1490 in trials comparing WS® 1490 to placebo.

| | Duration (weeks) | Change WS® 1490 | Change placebo | Ratio of means |
|---|---|---|---|---|
| This trial[a] | 4 (6) | 8.6 | 7.6 | 1.13 |
| Kinzler et al. (1991)[b] | 4 | 12.7 | 3.3 | 3.85 |
| Warnecke (1991)[b] | 8 | 25.6 | 7.7 | 3.32 |
| Volz and Kieser (1997)[b] | 25 | 21.0 | 16.2 | 1.30 |

[a] dosage: 150 mg/d; outcome measure: ASI total score
[b] dosage: 300 mg/d; outcome measure: HAM-A total score

exceeding two months (Kinzler et al. 1991; Warnecke, 1991), on the other hand, showed substantially larger treatment effects of WS® 1490 relative to placebo. The larger differences versus placebo could be a result of the higher dosage of the investigational drug. However, the smaller treatment group differences in our trial might also reflect a more general trend towards increasing 'placebo effects' in clinical trials in psychiatric indications (attributable to a 'therapeutic effect' of the increasingly complex trial procedures) that make superiority over placebo more and more difficult to prove (Montgomery, 1999a, b; Schweizer and Rickels, 1997).

The fact that the analysis of variance approach based on the differences versus baseline showed a clear advantage of WS® 1490 over placebo, whereas only a much smaller effect was discovered in the primary analysis based on the treatment end ratings alone, raises questions regarding the appropriateness of our primary endpoint. The analysis of variance revealed that the treatment effect was masked by large differences between the study centers although there was obviously no interaction between these two factors. The center differences therefore do not jeopardize the validity of the comparison between WS® 1490 and placebo, but point to certain idiosyncrasies regarding the rating of the over-all intensity of anxiety. Future trials should therefore place more emphasis on standardization of the ratings across the participating centers.

Another limitation regarding the interpretation of the efficacy data lies in the mixed population of our trial which represented a rather broad spectrum of neurotic anxiety disorders. In future trials, more specific indications might be preferable.

With only one comparatively trivial adverse event (tiredness) attributable to WS® 1490, the herbal extract was well tolerated. Notably, no adverse influence on hepatic enzymes was observed. However, the sample size of our trial and the comparatively short exposition to the investigational drug restrict safety conclusions that can be generalized onto other populations.

## Conclusion

In the patients participating in our trial 150 mg/d Kava extract WS® 1490 was effective in reducing the severity of symptoms associated with neurotic anxiety, albeit possibly not as effective as the 300 mg/d dosage investigated in previous trials. WS® 1490 was well tolerated.

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