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# Efficacy of a special Kava extract *(Piper methysticum)* in patients with states of anxiety, tension and excitedness of non-mental origin – A double-blind placebo-controlled study of four weeks treatment

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## Summary

In a randomized, placebo-controlled double-blind study two groups of 29 patients each with anxiety syndromes not caused by mental disorders were treated for four weeks with three daily doses of 100 mg of Kava extract WS 1490 (Laitan®) from *Piper methysticum* rhizoma or a placebo preparation.

Therapeutic efficacy was assessed by the Hamilton Anxiety Scale (main outcome variable), the Adjectives Check List and the Clinical Global Impression Scale (secondary target variables) after 1, 2, and 4 weeks of treatment.

The HAMA overall score of anxiety symptomatology revealed a significant reduction in the drug group compared with the placebo group after one week of treatment. The difference between the two groups of patients increased during the course of the study. The results of the secondary target variables were in agreement with the HAMA score and demonstrated the efficacy of WS 1490 in patients with anxiety disorders. No adverse reactions caused by the medication were noted during the four weeks WS 1490 was administered.

Key words: Anxiety syndrome, Kava extract WS 1490 (Laitan®), *Piper methysticum*, clinical pharmacodynamics.

## Introduction

The first scientific botanical description of *Piper methysticum* was made by Johann Georg Forster (1754–1794), who described the relaxing action of the Kava Kava liquid gained from the roots of this plant.

Due to its effect on the central nervous system (CNS), Kava already has long held great scientific interest in former times. Cuzent (1860), O'Rorke and Gobley (1860) presented the first phytochemical investigations. In an 1996 monograph Lewin combined findings of the botanics, chemistry, pharmacology, toxicology and the first findings of animal experiments. The question of the effective components of the kava extract has been clarified to a great extent.

The relaxing action of the Kava Kava beverage is produced by the so-called kava-lactones kavain, methysticin, yangonin, dihydrokavain, dihydromethysticin, and desmethoxyyangonin (Hänsel, 1964).

Animal experiments have shown the reticular formation of the brain stem to be their site of action. An essential difference between the mechanism of action of the kava-lactones and narcotics is that the lactones do not influence monosynaptic reflexes. Instead they cause a motor sedation and relaxation of the skeletal muscles while leaving breathing uninfluenced (Meyer and Kretzschmar, 1966).

An especially relaxing action, affective and muscular, with simultaneous stimulation of the thinking process and activity has been attributed to kavain (Kretschmer, 1970; Lehmann et al., 1989).

The psychotropic action of the kava-lactones have re-

ceived little clinical attention due to the rapid development of psychopharmacological therapy using synthetic preparations, especially tranquilizers of the benzodiazepine type, neuroleptics and antidepressants. But phytopharmaceuticals have gained more consideration recently, because synthetic psychopharmaceutical drugs frequently have side-effects that complicate treatments of several weeks duration.

Kava extract WS 1490 is a standardized special extract produced from the dried Kava Kava rhizome in a multistage procedure and standardized on 70 mg Kava-lactones. It contains the kava-lactones kavain, dihydrokavain, methysticin, dihydromethysticin, yangonin, and desmethoxyyangonin as active substances. One capsule with 100 mg dry extract contains 70 mg kava-lactones. According to animal experiments, the kava-lactones have a muscule relaxant, spasmolytic, local anesthetic and antiarrhythmic action (Shulgin, 1973; Meyer, 1966; Kretzschmar and Teschendorf, 1974; Kretzschmar and Meyer, 1967 and 1968; Hänsel and Haas, 1984). In clinical studies they show a clearly anxiolytic profile of action without any signs of addiction or dependence at therapeutic dosages (Bhate, 1988; Warnecke, 1986, 1989).

It was the aim of this study to investigate the clinical efficacy of WS 1490 in patients with states of anxiety, tension and excitedness of non-mental origin and to document its tolerance.

## Patients and Methods

The efficacy of WS 1490 was investigated in a clinical placebo-controlled double-blind study of four weeks duration. The concept of the study was in accordance with the principles of clinical investigation of drugs, as described in the "Bundesanzeiger" (Federal Law Gazette) No. 243 of 1987.

After providing detailed information and informed consent, 58 outpatients (43 females, 15 males) were included in the study. Twenty-nine patients each received 3 x 1 capsule of WS 1490 or placebo daily. The patients were assigned by numbers to either of the groups using randomized computer allocation. Verum and placebo were equal in color, odor and taste. Neither the patients nor the clinical investigator had any knowledge of the assignment until evaluation. Patients were selected according to the following criteria:

*Inclusion Criteria*

- Total Score of Hamilton Anxiety Scale (HAMA) more than 18 points,
- age between 18 and 60 years.

*Exclusion criteria*

- Tendency to suicide, endogenous depression, mental conditions of organic origin, psychoses of the schizophrenic type, and psychopathic disorders,
- syndromes of dementia,
- severe diseases of the kidneys, liver, lungs, heart, cardiovascular system as well as neoplasia, irrespective of its localisation,
- pregnancy,
- medication interfering with the assessment of efficacy and not included as comedication.

In addition to clinical findings, criteria of inclusion or exclusion were secured by means of the following questionnaires or procedures:

- Recording of patient histories to establish previous mental conditions and prevailing diseases according to ICD, as well as symptoms during the preceding few weeks,
- questionnaire of life history (Lazarus, 1973),
- Minnesota Multiphasic Personality Inventory (MMPI), short form, German edition (Gehring & Blaser, 1982).

To evaluate the therapeutic success, the following methods of investigation served as main and/or secondary variables and were recorded at the beginning of the study as well as after 7, 14, and 28 days.

*Main Outcome Variable*

*Total score of Hamilton Anxiety Scale (HAMA)*

The HAMA is an assessment scale of symptoms of anxiety to be rated by a physician. Its 14 items consider mental and somatic effects of anxiety (Hamilton, 1959, 1986). Each item is graded according to its severity from "absent" (0) up to "severe" (4). The grades of all 14 items are added up to a total score.

*Secondary Variables*

*HAMA Subscales*

According to factorial analyses, the 14 HAMA items form groups of two factors or subscales. The HAMA subscales "mental anxiety" and "somatic anxiety" were evaluated descriptively.

*Adjectives Check List (EWL)*

The EWL is a self-assessment scale. We used the scaled 60 items form (EWL-K, 1983), which was subscaled into six groups (performance-orientated activation, general deactivation, extra-/introversion, general well-being, emotional irritation, anxiety/depression).

*Clinical Global Impression Scale (CGI)*

The CGI scale (CIPS, 1986) focuses on three global aspects to evaluate medical therapy: the severity of illness, the therapeutic success and the therapeutic results in relation to side-effects.

*Fischer's Somatic or Adverse Experiences Checklist (FSUCL)*

The FSUCL is a scale to evaluate undesirable events in the course of treatment (Fischer-Cornelssen, CIPS, 1986) for rating by a physician or the attendant personnel. Six subscales are formed involving clinical symptoms.

*Concomitant Therapy*

As co-medication, all substances were excluded which might interfere with the assessment of efficacy, i. e. psychotonics, neuroleptics, antidepressants, tranquilizers, and beta-blockers. After withdrawal and until the start of the study, a wash-out period of at least five half-life periods of the preparation considered had to be observed.

*Evaluation*

The procedures of biometric evaluation were established prior to the start of the study according to the outcome measures specified in the study design. The three null hypotheses to be investigated statistically specify that the HAMA total scores of the verum group on the 28th, 14th or 7th days, respectively, are not smaller than those of the placebo group. These three hypotheses were evaluated within a sequentially testing procedure by means of the U-test (Sonnemann, Lehmacher, 1989).

The CGI variable was evaluated via the Chi-square test.

The evaluation considered all patient data at each of the time points during the study. As shown later, six patients dropped out without giving any reasons.

## Results

A total of 58 patients (29 verum, 29 placebo) were investigated; the groups were not different as to age, height, weight, duration of illness, HAMA scores, EWL scores, or severity of illness according to CGI item 1 *(Table 1)*.

Concerning the main target variable, the total score of the Hamilton Anxiety Scale, a difference between the therapy groups was found after only one week of treatment, with markedly lower mean scores under WS 1490 (x = 16.2/sd = 7.1) in comparison to placebo (x = 21.8/sd = 7.8). This difference increased during the course of treatment; the mean total score after four weeks being x = 12.6/sd = 8.6 for the WS 1490 group as opposed to the placebo group, which remained practically unchanged (x = 21.0/sd = 10.1) *(Fig. 1)*. At all three periods, the differences were statistically significant at $p < 0.02$.

Based on the subscales of the Hamilton Anxiety Scales "mental anxiety" and "somatic anxiety", developments comparable to the total score could be observed. In the WS 1490 group the mean score of "mental anxiety" dropped from an initial x = 15.3/sd = 3.9 to x = 7.6/sd = 6.1 after four weeks. In the placebo group this parameter showed only an insignificant change from x = 15.0/sd = 3.1 to x = 12.0/sd = 5.6. Developments are shown in *Fig. 2*. On day 1, the mean score of "somatic anxiety" in the verum group was x = 10.3/sd = 3.5 and in the placebo group x = 9.5/sd = 3.6 as opposed to x = 5.0/sd = 3.6 and x = 9.0/sd = 3.6, respectively, on day 28. The observed group differences were statistically significant at $p < 0.01$ *(Fig. 3)*.

The mean values of the self-assessed "performance orientated activation" increased markedly in the verum group *(Fig. 4)*. The grade of self-assessed 'anxiety/depression' dropped to a greater extent under WS 1490 than under placebo *(Fig. 5)*. The group differences were statistically significant ($p < 0.05$). The other subscales of the EWL showed no changes under WS 1490 in comparison to placebo.

The severity of disease as rated by the Clinical Global Impression Scale (CGI) decreased more significantly under WS 1490 than under the placebo *(Fig. 6, 7)*. After four weeks of treatment the severity of illness in the majority of patients was rated at 4 (only slightly ill), whereas the majority of the placebo group was rated at 6 (markedly ill). After the treatment, 15 patients of the verum group were not any more or only slightly ill, whereas only five patients of the placebo group could be categorized similarly. The variables "change of state" and "use/risk" index also changed in the course of the study in favor of the WS 1490 group.

No undesirable events as documented by FSUCL and UAW occurred during the four weeks of treatment. One patient of each group dropped out after two weeks, three patients of the verum group and one of the placebo group did not present themselves for final examination. Altogether, four patients of the verum group and two of the placebo group dropped out of the study without giving any reasons. There was no difference in the drop-out rate between the two groups. A drop-out due to accidental reasons must be assumed.

## Discussion

The importance of an efficient therapy for anxiety syndromes that carries as little risk as possible is demanded, because of the frequency of such pathological conditions. One large American "Epidemiological Catchment Area Study" found a six months' prevalence rate of 8.9% (Burke and Regier, 1988).

The tranquilizers, neuroleptics and antidepressants currently used to treat anxiety disorders frequently involve a risk of addiction or severe side-effects. Long-term therapy especially needs preparations with a good use/risk index, and this is where phytopharmaceuticals have increasingly gained attention in recent years. This study investigated the anxiolytic effect of WS 1490 in patients with states of anxiety, tension and excitedness of non-mental origin.

WS 1490 showed a good anxiolytic efficacy along with a

significant reduction of the total score of the Hamilton Anxiety Scale (HAMA) after only one week of treatment. The HAMA with its standardized assessment scales is a recognized method for evaluating states of anxiety and provides good opportunities for verifying the various symptoms and complaints of anxiety syndromes (Hamilton, 1981).

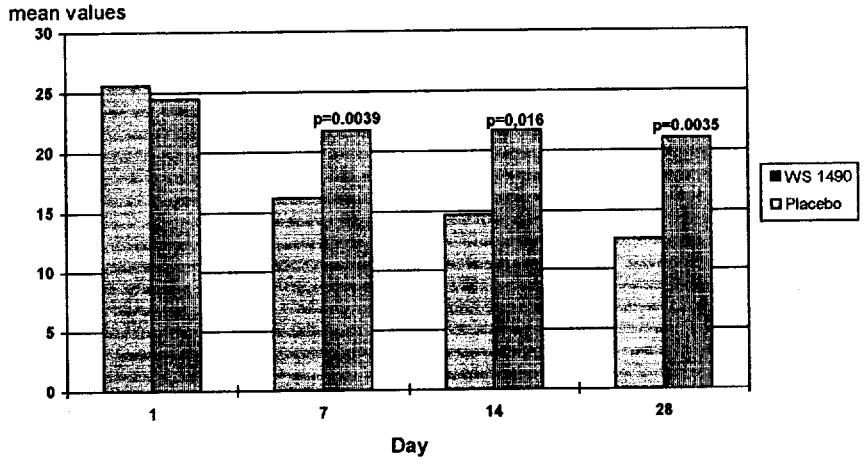
The results of the additionally evaluated scales (HAMA psychic anxiety, somatic anxiety, Adjectives Check List, EWL) agreed with the results of the total score. The comparison of the self-assessed grade of severity of the disease as an expression of the overall subjective impression of the patients revealed a tendency to lower grades of severity in patients treated with WS 1490 after four weeks of treatment.

It has been possible to confirm the anxiolytic effects of the kava lactones described in previous studies (Krach, 1986; Kretzschmar, 1974 and 1983; Bhate, 1989; Warnecke, 1989 and 1990) in the case of WS 1490, which is in agreement with more recent clinical investigations (Warnecke, Johnson, 1990). In neurophysiological investigations of patients being treated with WS 1490, Johnson found an EEG profile typical for anxiolytics.

The positive effects noticeable only after one week of treatment increased during the course of the four weeks of observation. Since no adverse drug reactions were produced during the entire course of this investigation, the use/risk index can be judged as good. Accordingly, WS 1490 is suitable for the general practitioner in treating states of anxiety, tension and excitedness.

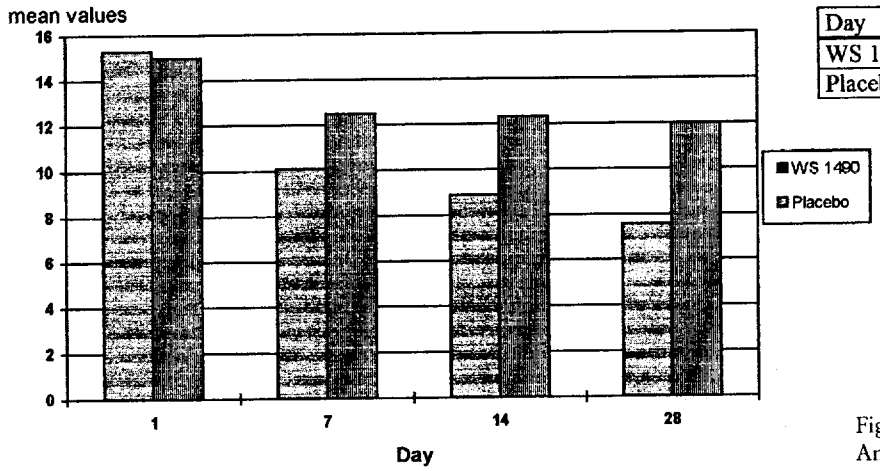
Table 1. Patient's data at the start of the study.

| | WS 1490 | | Placebo | |
|---|---|---|---|---|
| | x | sd | x | sd |
| Age (years) | 43.8 | 10.5 | 41.9 | 10.8 |
| Weight (kg) | 67.1 | 11.7 | 69.2 | 12.2 |
| Duration of illness (months) | 18.2 | 20.3 | 16.6 | 24.9 |
| HAMA score | 25.3 | 5.7 | 24.3 | 5.1 |
| *CGI-1* | N | | N | |
| Degree of severity: 5 | 8 | | 6 | |
| Degree of severity: 6 | 21 | | 23 | |



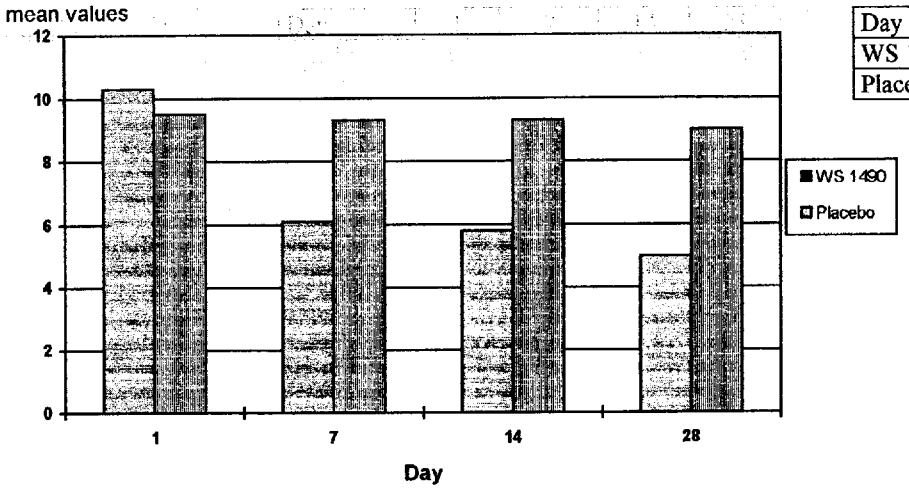

| Day | 1 | 7 | 14 | 28 |
|---|---|---|---|---|
| WS 1490 | 25.6 | 16.2 | 14.7 | 12.6 |
| Placebo | 24.5 | 21.8 | 21.7 | 21.0 |

Fig. 1. Hamilton anxiety Scale, Total Scores (mean values)



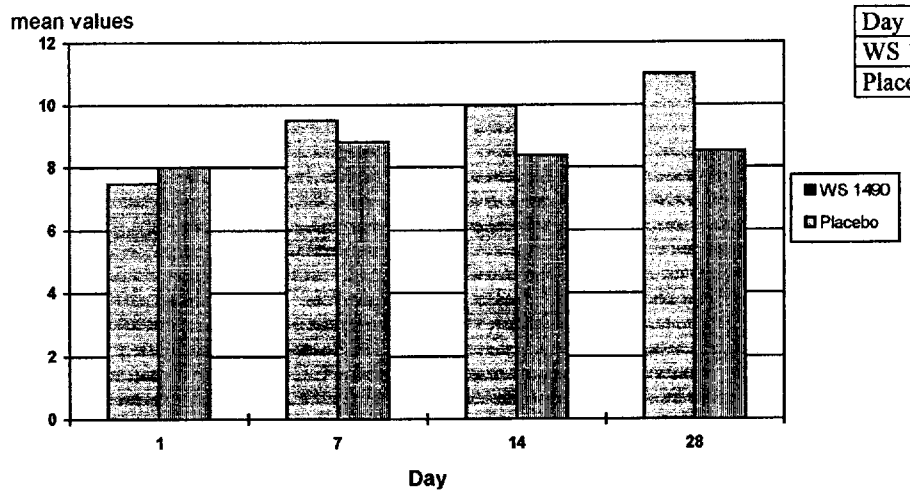

| Day | 1 | 7 | 14 | 28 |
|---|---|---|---|---|
| WS 1490 | 15,3 | 10,1 | 8,9 | 7,6 |
| Placebo | 15,0 | 12,5 | 12,3 | 12,0 |

Fig. 2. Hamilton Anxiety Scale, Mental Anxiety (means values)



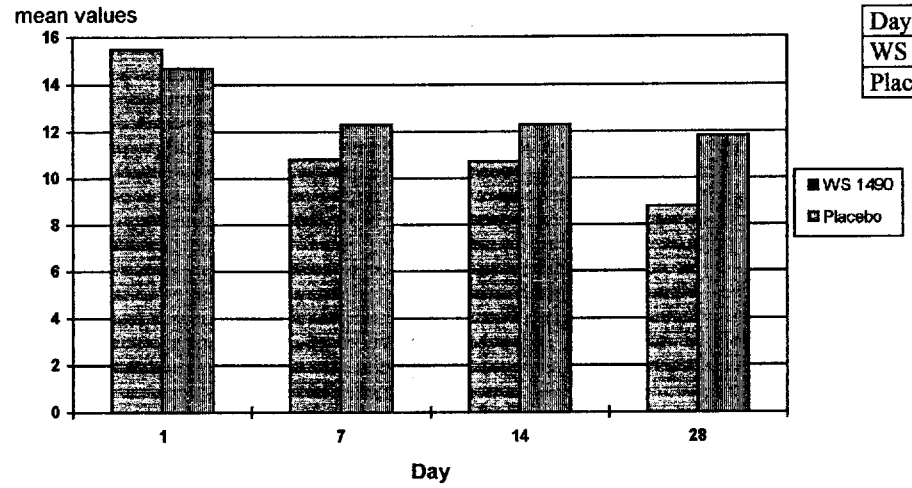

| Day | 1 | 7 | 14 | 28 |
|---|---|---|---|---|
| WS 1490 | 10,3 | 6,1 | 5,8 | 5,0 |
| Placebo | 9,5 | 9,3 | 9,3 | 9,0 |

Fig. 3. Hamilton Anxiety Scale, Somatic Anxiety (means values)



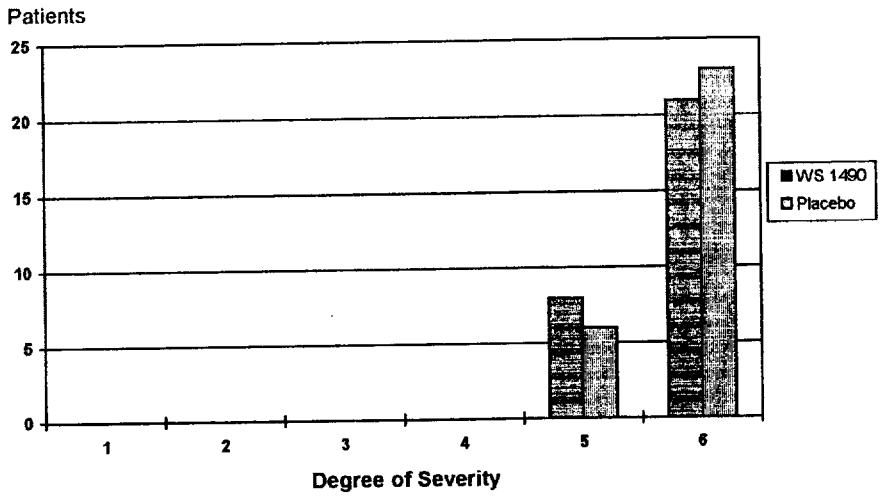

| Day | 1 | 7 | 14 | 28 |
|---|---|---|---|---|
| WS 1490 | 7,5 | 9,5 | 10,0 | 11,0 |
| Placebo | 8,0 | 8,8 | 8,4 | 8,5 |

Fig. 4. Adjectives Check List 'Performance-orientated Activation' (mean values)



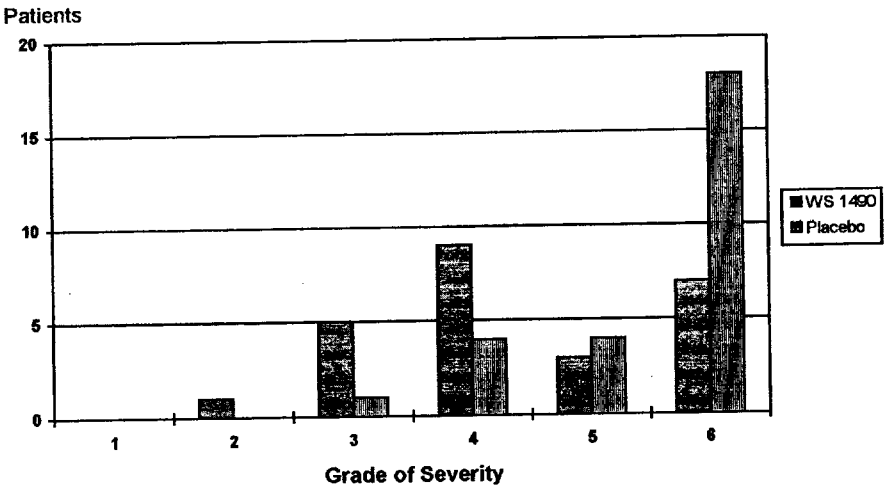

| Day | 1 | 7 | 14 | 28 |
|---|---|---|---|---|
| WS 1490 | 15,5 | 10,8 | 10,7 | 8,8 |
| Placebo | 14,7 | 12,3 | 12,3 | 11,8 |

Fig. 5. Adjectives Check List 'Anxiety/Depression' (mean values)




| Degree of Severity | 5 | 6 |
|---|---|---|
| WS 1490 | 8 | 21 |
| Placebo | 6 | 23 |

Fig. 6. Clinical Global Impression (CGI) at the start of study




| Degree of Severity | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|
| WS 1490 | 0 | 1 | 5 | 9 | 3 | 7 |
| Placebo | 0 | 0 | 1 | 4 | 4 | 18 |

Fig. 7. Clinical Global Impression (CGI) at the end of study (day 28)

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