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Comparative Efficacy and Safety of a Once-Daily Dosage of Hypericum Extract STW3-VI and Citalopram in Patients with Moderate Depression: A Double-Blind, Randomised, Multicentre, Placebo-Controlled Study

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Objective: The objective of this double-blind, randomised, placebo-controlled, multicentre clinical study was to demonstrate the non-inferiority and safety of the hypericum extract STW3-VI in a once-daily dosage regime in the treatment of moderate depression. During the 6-week treatment phase, the course of depression was documented by use of HAMD (items 1–17), the von Zerssen's Adjective Mood Scale (BfS) and the CGI scales. The primary objective of this 3-arm design study was to demonstrate the non-inferiority of hypericum extract STW3-VI (900 mg) to the SSRI citalopram (20 mg) and superiority of hypericum over placebo. **Methods:** Outpatients (N = 388) suffering from moderate depression were enrolled. The safety and tolerability of hypericum extract in comparison to citalopram and placebo was investigated on the basis of CGI, the occurrence of adverse events and the investigation of laboratory parameters and vital signs. **Results:** From almost identical baseline values of 21.9 ± 1.2 points (hypericum extract), 21.8 ± 1.2 points (citalopram) and 22.0 ± 1.2 points (placebo), the HAMD score was reduced to 10.3 ± 6.4 (hypericum extract), 10.3 ± 6.4 (citalopram) and 13.0 ± 6.9 (placebo), respectively. Based on this data, the statistical significant therapeutic equivalence of hypericum extract STW3-VI to citalopram ($p < 0.0001$) and the superiority of this hypericum extract over placebo ($p < 0.0001$) was demonstrated. At the end of treatment 54.2% (hypericum extract), 55.9% (citalopram) and 39.2% (placebo) of the patients were assessed as therapy responders. The secondary efficacy parameters, change in BfS, CGI and amount of therapy responders showed that the hypericum group was not statistically different from the citalopram group, and significantly superior to the placebo group. Significantly more adverse events with "certain", "probable" or "possible" relation to study medication were documented in the citalopram group (hypericum: 17.2%, citalopram: 53.2%, placebo: 30%). In most cases, the investigators assessed the tolerability of hypericum extract, citalopram and placebo as "good" or "very good". **Conclusion:** The non-inferiority of hypericum extract as compared to citalopram and the superiority of both active compounds to placebo were demonstrated, as well as a better safety and tolerability of hypericum extract in comparison to citalopram. These results revealed that hypericum extract STW3-VI is a good alternative to chemically defined antidepressants in the treatment of outpatients with moderate depression.

Introduction

Depression is one of the most frequently occurring psychiatric disorders treated by general practitioners. In recent years, the diagnosis of depression and depressive mood has continuously increased in industrial countries [16]. The first pan-European survey of depression in the European community (DEPRES I) demonstrated that 17% of the general population suffer from depression. More than two-thirds of depressed subjects (69%) did not receive any psychopharmacological treatment and when drug

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therapy was prescribed (31%), only 25% of these subjects were given antidepressant drugs [19]. Due to the complexity of the diagnosis and the treatment options it seems difficult to choose the appropriate medication. Therefore, general practitioners prescribe antidepressants only reluctantly, particularly because of frequent side effects. Significantly more respondents treated with a selective serotonin reuptake inhibitor (SSRI) found that their treatment made them feel more like their normal self than those treated with a tricyclic antidepressant, and fewer reported treatment-related concentration lapses, weight problems, and heavy headedness [17,41]. However, even with SSRIs, side effects frequently occurred such as sexual dysfunction, insomnia, nausea and vomiting. Up to 30% of patients suffer from adverse reactions and discontinue treatment. Antidepressants with fewer side effects and moderate costs would be a useful supplement for the outpatient treatment of depression. Hypericum extract is such an alternative to chemically defined antidepressants such as TCAs, SSRIs and monoamine oxidase inhibitors (MAOIs). In recent years hypericum has been approved for the treatment of mild to moderate depression. In comparison to synthetic antidepressants lower rates of side effects and good compliance were observed with St. John's Wort extracts [38].

Over the last 10 years, the antidepressive effect of hypericum extract has been demonstrated in several active- or placebo-controlled studies [13,20,27,30,34,36,37,40,42,43]. The daily dose used in these studies, administrated mainly in a 2–3 times daily dose regime, varied from 600 to 1200 mg. Due to the long elimination half-life times of the main active ingredients of *Hypericum perforatum*, such as hypericin, pseudohypericin and hyperforin [15,32,33], a compliance facilitating once-daily administration of hypericum extract is possible.

If hypericum extract is used according to instructions, side effects are rare. The frequency of side effects did not differ from placebo and was much lower from that of classic antidepressants. In pale skinned persons a few cases of light sensitivity of the skin (photosensitivity) were reported [4,15]. In addition, hypericum extracts interact with various drugs, most likely related to the induction of cytochrome P450 isoenzymes and/or P-glycoprotein, which may lead to a reduction in plasma concentrations and therefore in diminished therapeutic efficacy of concomitant medications. Nevertheless, clinical studies have demonstrated that hypericum extracts are safe and well tolerated.

The investigational drug of the present study was STW3-VI, a standardised extract of 900 mg of the herb *Hypericum perforatum*, which is registered under the trade name Laif 900® for the treatment of depression. This dosage was chosen, as the most frequently investigated daily dose of hypericum extract in the treatment of mild to moderate depressive disorders is 3 × 300 mg (corresponding to 900 mg/d). The reference drug citalopram is a potent and highly selective serotonin reuptake inhibitor [with a half-maximal inhibitor concentration (IC_{50}) of about 1 nM]. Citalopram is one of the most effective and best-tolerated SSRIs available. The most commonly observed adverse events associated with citalopram are sweating, somnolence, nausea, tremor, dry mouth and asthenia. The antidepressant effect of citalopram is well documented by a number of controlled studies comparing its efficacy with that of placebo or standard antidepressants [1,14,28]. Therefore, citalopram is accepted as standard medication in the antidepressive therapy of outpatients.

To date no comparative study of hypericum extract and citalopram in the treatment of patients with moderate depression has been published. The purpose of this trial was to demonstrate for the first time the comparable efficacy of the hypericum extract to citalopram after short-term treatment of patients with moderate depression with a once-daily dose regimen. Additionally, the superiority of hypericum extract STW3-VI to placebo should be demonstrated. Moreover, the favourable safety and tolerability profile of hypericum extract should be shown.

Patients and Methods

This Phase III study was carried out in accordance with the Principles of Good Clinical Practice (GCP) for the conduct of clinical trials with drugs in humans in the EU and of the Note for Guidance on clinical investigation of medicinal products in the treatment of depression (CPMP/EWP/518/97/2002), the ICH Guidelines, and the ethical principles that have their origin in the Declaration of Helsinki. The required documents were submitted to an independent Ethics Committee and approved by positive vote.

Selection of Patients

Primary care physicians (general practitioners and internists) recruited the patients in the period from October 2002 to May 2003. Female and male outpatients with a moderate depressive episode and with the following inclusion criteria were included in the study: written consent after comprehensive explanation of the content, significance and scope of the clinical trial by the investigator; age: 18–70 years; females taking adequate contraceptive or without child-bearing potential; patients having depression with a score of 20–24 on the Hamilton Depression Scale (HAMD, items 1–17) [9]; and diagnosis of moderate depression (first manifestation or recurrent depressive disorder) defined by ICD-10 F32.1 or F33.1 [12] according to DSM-IV major depressive episode (296.2×) and recurrent major depression (296.3×) [5].

In addition to general exclusion criteria, the following anamnestic exclusion criteria were applicable: diagnosis of resistance to depression treatment; known schizophrenia; psychosis or dementia; depressive mood due to a serious general disease; known hypersensitivity to study medication; known photosensitivity; specific antidepressant psychotherapy during the last two months or treatment with psychoactive drugs (antidepressants, neuroleptic drugs, antidementive drugs, anxiolytic drugs etc.) during the last 3 weeks (6 weeks for fluoxetine) prior to study enrolment; and determined suicidal tendency by scores of > 2 in item 3 of HAMD scale or known attempted suicide.

Study Design

The study was designed as a double-blind, randomised, multicentre study to compare the efficacy and safety of hypericum extract STW3-VI to citalopram and to placebo in outpatients with moderate depression. The study period per patient was six weeks from enrolment to study end. During this time, the patients undertook four visits (including enrolment). The efficacy

of the study drugs was assessed by documentation of the course of depression using rating scales, such as the Hamilton Depression Scale (HAMD), the Von Zerssen's Adjective Mood Scale (BfS) [8], and the Clinical Global Impression (CGI). The investigators were experienced in the application of the study's diagnostic criteria and rating scales. Uniform standards of judgment were ensured by special rater training.

The time-points for examinations were all study visits (days 0, 7, 21 and 42). The compliance of the patients was checked and documented at the end of study by counting the returned tablets. The study course is shown in Table **1**.

According to a randomisation schedule using the randomisation program IDV-Rancode 3.6, patients were chronologically randomised by the investigators to treatment groups by assigning them the lowest yet unassigned treatment number available at the trial centre.

Investigational Treatments

STW3-VI is a hydroalcoholic extract from the herb *Hypericum perforatum*. The 900 mg extract/tablet was produced from 4 g of dry plant material, which corresponds to the maximum recommended daily dose [6,18]. Citalopram, in a dosage of 20 mg, is the recommended dosage for treatment of depression and is considered to be sufficient for outpatients [1,14,22,26]. The medications were given once daily in the morning. Due to the different visual appearance of hypericum extract and citalopram the double-dummy technique was used to guarantee complete blinding for both investigator and patient at any time in the trial.

Study Objectives for Efficacy and Safety

The primary objective of the study was to demonstrate the non-inferiority of hypericum extract STW3-VI to citalopram and the superiority of hypericum extract to placebo in the treatment of moderate depression as evidenced by the change in the Hamilton Depression scale score (HAMD) after a 6 week treatment period. Based on clinical considerations the pre-defined non-inferiority boundary δ between treatment groups was 3 ($\delta = 3$ points on the Hamilton scale). As secondary parameters, the efficacy parameters BfS and CGI as well as safety and tolerability of hypericum extract STW3-VI in comparison to citalopram and placebo were investigated.

In addition, treatment success was evaluated by means of response rates. Therapy responders were defined as patients with a HAMD score of < 10 after treatment or an improvement of the initial HAMD score of at least 50%. Patient's judgement was measured with BfS scale. Tolerability was assessed by the investigators and evaluated on the basis of CGI, the occurrence of adverse events and the investigation of laboratory parameters and vital signs.

Statistical Analysis

Appropriate descriptive univariate statistics were calculated for all observed variables. The statistical evaluation, in line with the distribution of the respective parameters, was carried out by analysis of covariance models (continuous data) with the factors, treatment and centre, as well as the covariate baseline value and with logistic regression models using the factors, treatment and centre (categorical data). Due to multiplicity (two primary objectives), the α-level was adjusted to $\alpha/2$ (Bonferroni correction).

The tests for superiority were carried out on the Intention-to-treat (ITT) population, the test for non-inferiority on the Per-Protocol (PP) population.

To validate the clinical study results concerning non-inferiority, the hypothesis of superiority of citalopram over placebo was tested. The null hypothesis of equivalence was tested. This test was carried out on a two-sided $\alpha/2$ level of 0.025 [the α for two-sided tests of 0.05 was divided by two (Bonferroni correction) due to the existence of two main objectives].

The hypothesis of therapeutic non-inferiority of hypericum extract to citalopram with the non-inferiority boundary $\delta = 3$ was tested one-sided using the null hypothesis of superiority of citalopram over hypericum. The test problem was analysed with an $\alpha/2$ level (type I error) of 0.0125 and the confidence interval was estimated. In cases of missing data, the LOCF approach (Last Observation Carried Forward) was applied.

For the second primary objective, the hypothesis of superiority of hypericum extract over placebo was assessed. Again, the null hypothesis of equivalence with a two-sided α of 0.025 was tested. The results were supplemented by point estimates for the treatment differences (LS means) and the corresponding one-sided 98.75% or two-sided 97.5% confidence intervals. To assess robustness of the test results, the analyses described were also carried out on the PP or ITT population, respectively. Analyses of the secondary efficacy parameters were based on the ITT population and used a two-sided α level of 5%.

Accounting for an additional number of around 20% drop-outs and non-evaluable patients because one of the two main analyses is based on the PP population, a total sample size of 390 patients had to be randomised, assuming an effect size of 0.5 between active drugs and placebo. The block size was six.

Table **1** Efficacy and Safety Measurements Assessed (Flow Chart)

	Visit 1 Day 0	*Visit 2 Day 7 (± 3)*	*Visit 3 Day 21 (± 3)*	*Visit 4 Day 42 (± 3)*
In- and exclusion criteria				
Patient information and consent				
Physical examination/ vital signs				
HAMD, BfS, CGI	X	X		
Laboratory findings	X			X
Concomitant diseases/ Concomitant medication				
Dispensing of medication				
Return of medication				
Compliance check				
Documentation of adverse events				
Assessment of efficacy and tolerability				

Results

At 21 centres, 388 outpatients aged 18 to 74 years with moderate depression were included in the ITT population. Considering various protocol violations 312 patients could be included in the PP population. From the 388 (312) patients in the ITT (PP) population, 131 (103) patients were treated with hypericum extract, 127 (104) with citalopram and 130 (105) with placebo. Unless otherwise marked, all data and results presented are based on the ITT population. For detailed patient distribution see Fig. **1**.

Patient Characteristics

For all demographic variables, the p-values for comparison of the treatment groups at the beginning of treatment were above 0.05 ($p = 0.2223$ to 0.8030). The demographic data is summarised in Table **2**. No differences between treatment groups were found.

The first manifestation of depression had been observed, on average, 35.9 months ago. Due to the exclusion criterion (no treatment with psychoactive drugs in the three weeks prior to inclusion), a high number of patients (59%) were not treated with antidepressant medication in the current episode. For 29.4% of the patients, depression in the family was documented. There was no significant difference between treatment groups regarding duration of depression, medical pre-treatment and depression in the family.

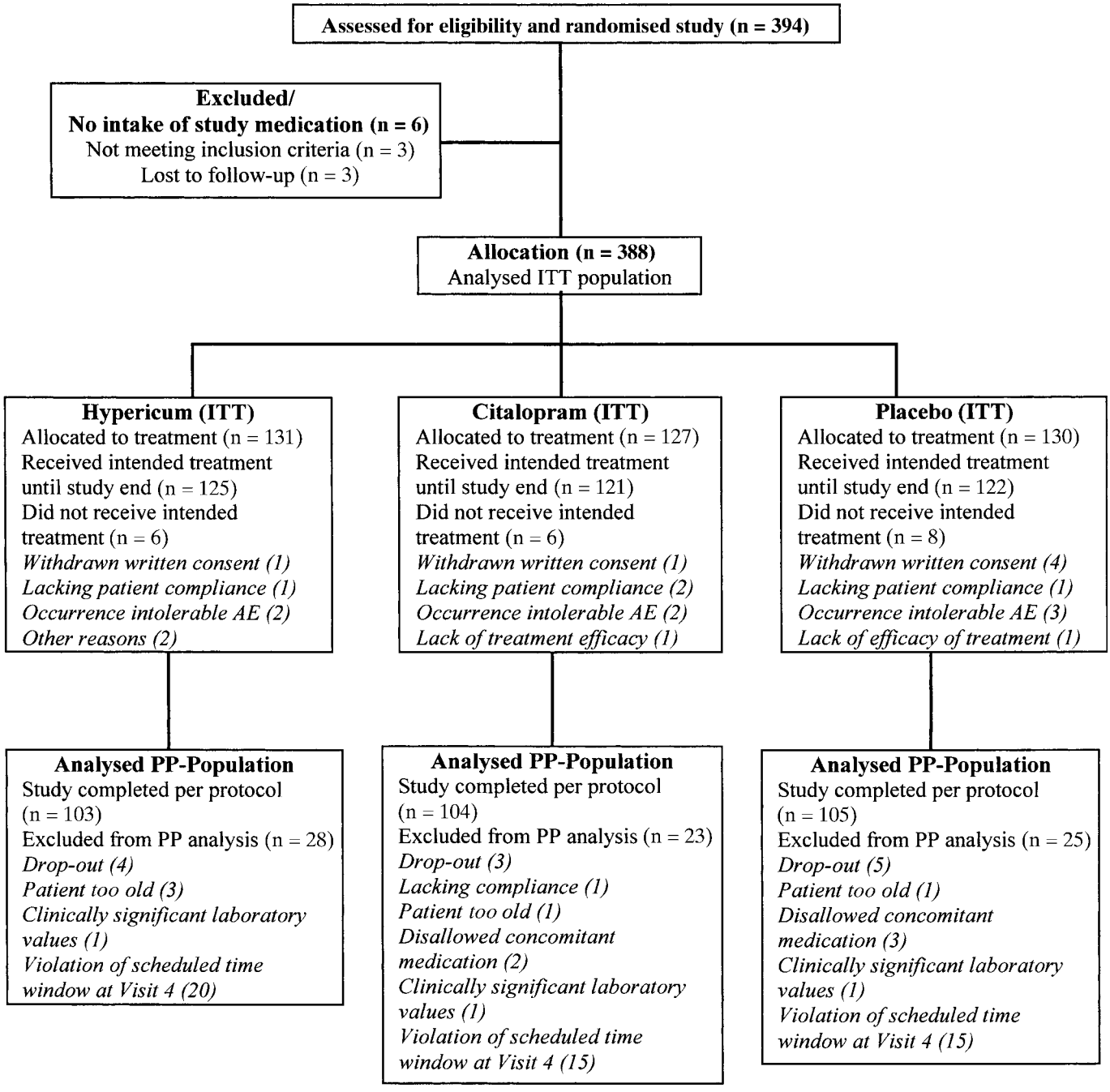

Fig. **1** Distribution of patients.

Table **2** Demographic data (ITT population)

	Hypericum (N = 131)	*Citalopram (N = 127)*	*Placebo (N = 130)*	*Test for baseline comparability*
Age [years]*	50.8 (12.1)	49.3 (10.7)	49.4 (12.7)	p = 0.3367
Gender [%]				p = 0.2223
Female	65.6	64.6	73.1	
Male	34.4	35.4	26.9	
Body height [cm]*	169.1 (8.9)	169.0 (8.1)	167.8 (8.5)	p = 0.3065
Weight [kg]*	75.6 (14.3)	76.8 (13.0)	75.2 (16.2)	p = 0.7161
BMI [kg/m^2]*	26.4 (4.3)	26.8 (4.0)	26.7 (5.5)	p = 0.8030
Duration of depression [months]*	36.4 (45.5)	37.3 (50.4)	34.2 (42.0)	p = 0.8451
Medical pre-treatment [%]	38.2	41.7	43.1	p = 0.6687
Depression in family [%]	33.6	27.6	26.9	p = 0.2803

*The values are expressed as mean (SD)

Results of Efficacy

Hamilton Depression Scale (HAMD)

The improvement of the HAMD score in both active treatment groups was almost identical, with a decrease of 11.6 in the hypericum group from 21.9 ± 1.2 points (median = 22.0) at treatment start to 10.3 ± 6.4 points (median = 9.0) at the end of treatment (LOCF) and a decrease of 11.5 points in the citalopram group from 21.8 ± 1.2 points (median = 22.0) to 10.3 ± 6.4 points (median = 10.0). Placebo showed a less pronounced effect with a drop of 9.0 points from 22.0 ± 1.2 (median = 22.0) to 13.0 ± 6.9 (median = 14.0) (Table **3** and Fig. **2**). The superiority of citalopram to placebo was highly significant (p < 0.0001, ITT). The null hypothesis of equal efficacy of citalopram and placebo could be rejected. The two-sided 97.5% confidence interval for treatment difference reached from –4.25 to –1.25 (median 2.75). The test of non-inferiority of hypericum extract STW3-VI to citalopram showed a highly significant result (PP population). The one-sided 98.75% confidence interval for treatment difference reached from –∞ to 1.93, excluding '3', the boundary for non-inferiority. The maximum superiority of hypericum was found to be 1.47 (two-sided 97.5% confidence interval). Finally, the question of superiority of hypericum extract to placebo was assessed (ITT population). The two-sided 97.5% confidence interval for treatment difference reached from 1.25 to 4.22 (median 2.73). The hypothesis of equal treatment effects was rejected with a p-value of < 0.0001, i.e. the alternative hy-

Table **3** HAMD Score during the 6 week course of study (ITT population, HAMD N = 388, BfS N = 301) values are expressed as mean (SD) and as median for HAMD. The CGI degree of severity shows the percentage of patients rated as moderately, markedly or severely ill. In the overall assessment of change in patient's condition the percentage of patients rated as much and very much improved was pooled. The therapeutic effect shows the percentage of patients rated as very good

	HAMD			*BfS*
	Mean	*Median*	*Min-Max*	*Mean*
Hypericum				
Baseline	21.9 (1.2)	22.0	20.0 – 24.0	35.9 (9.7)
Day 7	18.7 (4.0)	20.0	6.0 – 24.0	32.0 (12.5)
Day 21	13.5 (5.7)	13.0	2.0 – 27.0	27.7 (11.5)
Study end (LOCF)	10.3 (6.4)	9.0	0.0 – 29.0	21.1 (11.6)
Day 0 to Study end (LOCF)	11.6 (6.3)	13.0	–7.0 – 24.0	14.7 (13.5)
Citalopram				
Baseline	21.8 (1.2)	22.0	20.0 – 24.0	34.8 (11.6)
Day 7	18.3 (4.2)	19.0	6.0 – 24.0	31.9 (12.8)
Day 21	13.7 (5.8)	14.0	1.0 – 25.0	27.1 (12.4)
Study end (LOCF)	10.3 (6.4)	10.0	0.0 – 29.0	21.3 (11.6)
Day 0 to Study end (LOCF)	11.4 (6.5)	12.0	–8.0 – 24.0	13.2 (14.0)
Placebo				
Baseline	22.0 (1.2)	22.0	20.0 – 24.0	33.8 (11.8)
Day 7	18.7 (4.3)	20.0	5.0 – 25.0	32.6 (11.5)
Day 21	15.3 (6.1)	16.5	0.0 – 26.0	29.9 (11.5)
Study end (LOCF)	13.0 (6.9)	14.0	0.0 – 26.0	27.4 (12.8)
Day 0 to Study end (LOCF)	9.0 (6.8)	9.0	–4.0 – 22.0	6.1 (12.6)

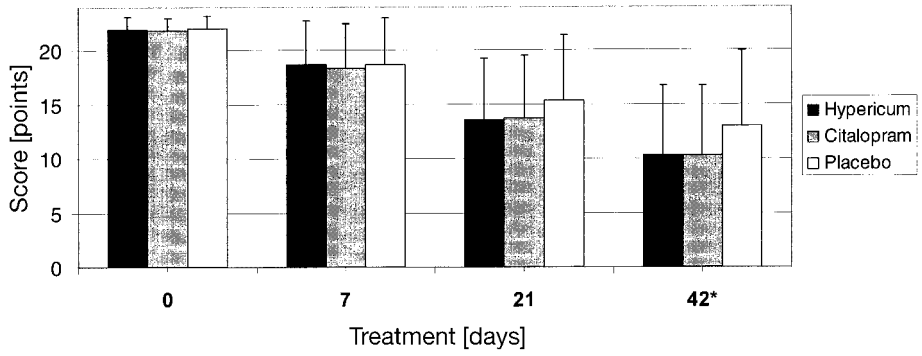

Fig. **2** Decrease of HAMD score during the course of study (Mean ± SD, ITT population). *Data at day 42 was estimated using the LOCF approach.

pothesis of superiority of hypericum extract over placebo was accepted.

To prove the robustness of the results, the analyses were repeated for the PP population (tests for superiority) and the ITT population (test for inferiority), respectively. The test results confirmed the results described above with the same degree of significance.

In summary, these data verified that the hypericum extract STW3-VI is not inferior to the SSRI citalopram and placebo is not as equally effective as hypericum extract.

Secondary Efficacy Parameters

Treatment success (responders) was assessed by reaching a HAMD score of < 10 or an improvement of the initial HAMD score of at least 50%. After the end of treatment, 54.2% of the patients treated with hypericum extract and 55.9% of the patients treated with citalopram were assessed, but only 39.2% of the patients in the placebo group were assessed as responders (ITT population). In the logistic regression model, the overall treatment effect (differences between treatment groups) was proved to be significantly different ($p = 0.0009$). The pair-wise comparisons demonstrated significant superiority of hypericum extract and citalopram to placebo ($p = 0.0026$ and $p = 0.0006$, respectively), but no significant difference between the active compounds ($p = 0.6252$). The point estimators for the odds ratio were 0.398 and 0.343 with corresponding two-sided 95% confidence intervals of (0.219, 0.725) and (0.187, 0.631). The response rates at the different visits were also comparable in both active treatment groups (Fig. **3**). The analysis of the PP population confirmed the results of the ITT population.

The assessment of BfS scales, which were completed independently by the patients showed a downward linear improvement with time (Table **3**). The overall difference between treatment groups regarding the last value under therapy was significant in the analysis of covariance model ($p < 0.0001$). In line with the other findings, the pair-wise comparisons proved the superiority of hypericum extract and citalopram to placebo (both $p < 0.0001$). The results of the ITT population were verified in the PP population.

Other acute phase outcomes such as the CGI scores items – severity of illness, global improvement and therapeutic effect – showed similar results. At the end of therapy the differences between the three treatment groups were statistically significant ($p < 0.0001$). In addition, the pair-wise comparison of hypericum extract and citalopram and of both to placebo was also significant ($p < 0.001$). The assessment of the PP population confirmed the ITT results. Results of CGI assessment are summarised in Table **4**.

Safety Evaluation

Adverse Events (AE) and Tolerability

All patients receiving study medication were included in the safety analysis (ITT population, n = 388). Altogether, 58 adverse events were documented for 39 patients (29.8%) in the hypericum group, 94 adverse events for 53 patients (41.7%) in the citalopram group and 70 adverse events for 46 patients (35.4%) in the placebo group. Interestingly, the greatest differences in the AE rate were observed in the system organ classes "gastrointestinal disorders" and "nervous system disorders", which resulted in a lower incidence of AEs in the hypericum group than in the placebo group. Severe intensity of the adverse effects was documented only for 2.3% of the AEs (hypericum and placebo: 1, citalo-

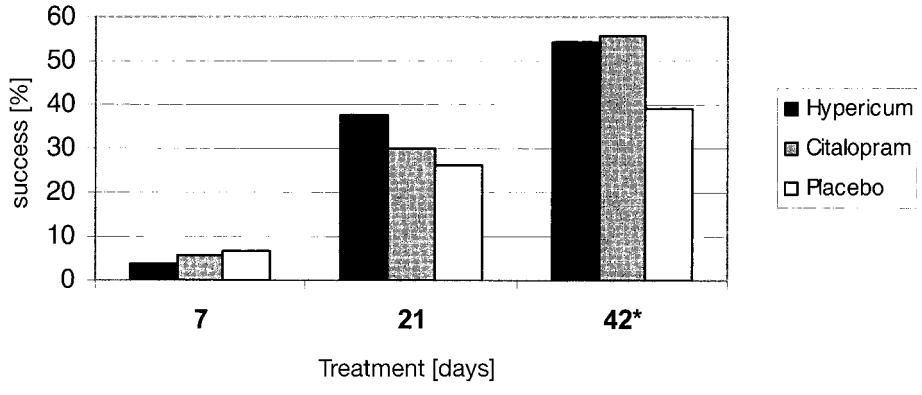

Fig. **3** HAMD score: Responder (N = 388, ITT population). *Data at day 42 was estimated using the LOCF approach.

Table **4** CGI Score during the 6 week course of study (ITT population, N = 388). The degree of severity shows the percentage of patients rated as moderately, markedly or severely ill. In the overall assessment of change in patient's condition the percentage of patients rated as much and very much improved was pooled. The therapeutic effect shows the percentage of patients rated as marked and moderate

	Clinical Global Impression								
	Severity			*Improvement*			*Therapeutic effect*		
	Hypericum	*Citalopram*	*Placebo*	*Hypericum*	*Citalopram*	*Placebo*	*Hypericum*	*Citalopram*	*Placebo*
Baseline	87.7	92.9	92.3	–	–	–	–	–	–
Day 7	82.1	85.7	86.6	10.6	8.0	4.7	12.4	10.3	6.3
Day 21	57.6	62.3	69.4	45.7	40.2	30.7	48.0	40.1	31.5
Study-end (LOCF)	35.7	41.2	57.9	65.1	67.9	54.0	66.7	70.6	43.7
Difference Baseline/Day 7 versus study-end	52.0	51.7	34.4	54.5	59.9	49.3	54.3	60.3	37.4

pram: 3). Furthermore, the investigator's assessment concerning the relation of AEs to study medication revealed a much lower number of AEs with a "certain", "probable" or "possible" relation to study medication in the hypericum group (17.2%) than in the other groups (53.2% citalopram group and 30.0% placebo group) (see Fig. **4**).

A much lower number of AEs with certain relation to study medication in the hypericum group (3.4%) and the placebo group (5.7%) than in the citalopram group (10.6%) was observed.

In four patients of the hypericum group (6.9%), in 11 patients of the citalopram group (11.7%) and in 6 patients of the placebo group (8.6%) the adverse events led to study discontinuation (total 21 patients, 9.5%) (see also Table **5**).

Altogether, 6 serious adverse events (SAEs) were documented (citalopram: 2, placebo: 4). One patient in the placebo group suffered from angina pectoris, another one was hospitalised for division of an intestinal adhesion, one with appendicitis and one with general anxiety disorders. Treatment was discontinued in all of these patients. In the citalopram group, study medication was discontinued in one patient after being admitted to a hospital due to serious depression with generalised anxiety disorder. One patient was hospitalised with a lesion of the brachial plexus and intake of medication was interrupted for six days. Regarding these patients no causal relationship to study medication was seen.

In addition, no interactions of hypericum extract and citalopram with concomitant medication was documented.

In most cases, the tolerability of study medication was assessed by the investigators at study end as "very good" or "good". Per visit, the maximum number of patients with moderate and poor tolerability of treatment was three patients (2.3%) in the hypericum group, twelve patients in the citalopram group (9.5%) and two patients (1.5%) in the placebo group. After 42 days, the tolerability was rated as "very good" or "good" in all of the patients in the hypericum group, whereas "moderate" or "poor" tolerability was observed in 11% patients in the citalopram group and in 2.3% patients in the placebo group (ITT population).

At the final study day (day 42) these differences in global assessment of tolerability between the treatments were proved to be statistically significant in a logistic regression model. The overall

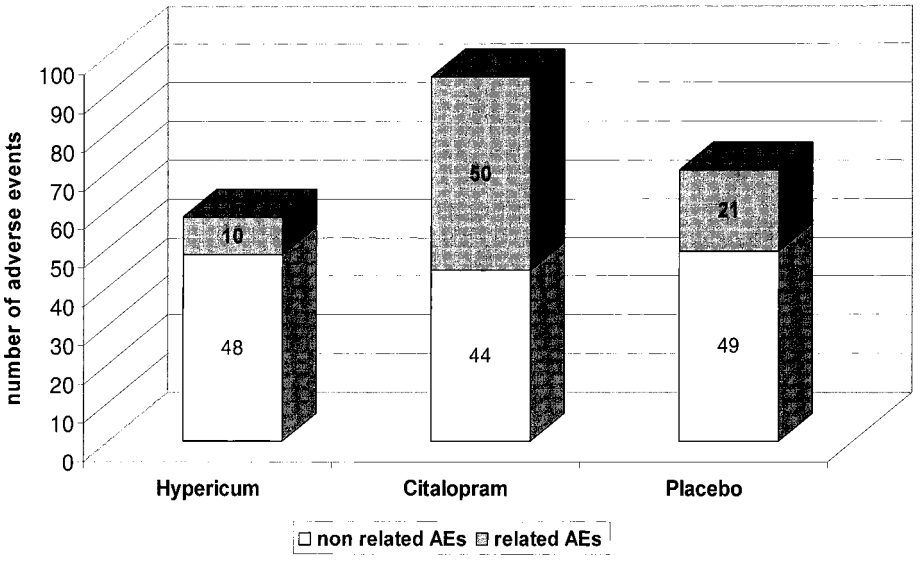

Fig. **4** Number of adverse events nonrelated (light colour) and in relation (dark colour) to study medication (ITT population).

Table **5** Number of adverse events by system organ class in relation to study medication (ITT population)

Adverse Events by system organ class (multiple mentions possible)	*Hypericum*		*Citalopram*		*Placebo*	
	N	*related*	*N*	*related*	*N*	*related*
All patients with AEs	39	7	53	27	46	14
Total number of AEs	58	10	94	50	70	21
Infections and infestations	20	0	17	1	17	0
Gastrointestinal disorders	11	6	23	20	20	9
Ear and labyrinth disorders	2	1	11	11	6	4
Nervous system disorders	1	0	9	5	10	7
Musculoskeletal and connective tissue disorders	6	0	5	1	3	0
Skin and subcutaneous tissue disorders	4	1	6	3	3	1

p-value for treatment differences was p = 0.0022 and also the pair-wise comparisons of hypericum against citalopram and placebo reached statistical significance (p = 0.0005 and p = 0.0234, respectively).

Vital Signs

For assessment of safety and tolerability of study medication, blood pressure and heart rate were measured and documented at each visit. Relevant findings were not reported to either the patients or the physician or the involved study staff. In addition, evaluation of the laboratory values documented at study end showed no clinically significant changes compared to baseline values.

Discussion

Due to the high number of prescriptions and of frequent OTC-use of hypericum in Germany for the treatment of mild to moderate depression, the question about the efficacy and safety of hypericum extract preparations has become of more interest. Hypericum extracts are potent inhibitors of the synaptosomal reuptake of the three neuronal transmitters noradrenaline, serotonin and dopamine while chemically defined antidepressants inhibit the uptake of only one or two neurotransmitters [24]. Clinical pharmacological studies in healthy volunteers investigating the effect of hypericum extract on CNS activity have shown an antidepressant effect as evidenced by increased wakefulness. The observed effects are similar to the efficacy profile of imipramine [27]. Over the last decade, the antidepressant effect of hypericum has been demonstrated in several active and placebo controlled studies in more than 3,000 patients [20, 34, 35, 42]. However, no study investigated the once-daily administration of hypericum extract in moderate depression comparing the efficacy and safety to the highly effective SSRI citalopram and to placebo as well.

Concerning the efficacy variables investigated, no significant differences were seen between patients treated with hypericum extract STW3-VI and patients treated with citalopram in the present study. The non-inferiority of hypericum extract to citalopram and the superiority of both to placebo were demonstrated, as well as a better safety and tolerability of hypericum extract in comparison to citalopram. The mean of the HAMD score decreased from almost identical initial values at baseline (21.9 points in the hypericum group and 21.8 points in the citalopram group) to 10.3 points in both active treatment groups. For patients treated with placebo, the mean value of the HAMD score decreased from 22.0 points at baseline to 13.0 points (last value of the 6-week treatment period).

Data published over the last decade confirmed that citalopram is superior to placebo in the treatment of depression, possess similar efficacy as the tricyclic and tetracyclic antidepressants and as other SSRIs, and is safe and well tolerated in the therapeutic dose of 20 mg/day [14]. The results received in the present study confirmed recent data observed in depressed patients [10]. During treatment, a decrease in the total score on the HAMD (21 items) from a mean initial value of 21.5 ± 2.9 prior to therapy, 14.5 ± 2.9 ($p < 0.001$) after 4 weeks of treatment and to 9.9 ± 3.1 ($p < 0.001$) after 8 weeks of treatment was found. There were 9 (20.9%) responders after 4 weeks of treatment and 28 responders (65.1%) after 8 weeks, all of them with decrease on the HAMD (21 items) greater than 50%.

These results are almost identical to the results of a recent active-controlled long-term study, with a once-daily dosage of 612 mg hypericum extract [7]. To summarize, in this and the present clinical trial the non-inferiority of hypericum extract to sertralin and to citalopram could be shown. These results confirm that hypericum extract is a therapeutic alternative for the treatment of moderate depression with SSRIs. Compared with the results of another recent study, which showed no significant difference in HAMD score of hypericum- and sertraline-treated patients [3], the findings of this report revealed to be an important basis for the role of hypericum extract in treating patients with depressive symptoms.

A study of the Hypericum Depression Trial Study Group [11] examined the efficacy of hypericum extract (LI 160) in comparison to the SSRI sertraline and placebo in major depressive disorder in a 3-arm clinical trial and found that neither sertraline nor hypericum extract was significantly different from placebo on the two primary outcome measures, the HAMD scale and the CGI scale. This shows the importance of a third arm with an active comparator.

However, the low assay sensitivity of this trial and the high overall placebo response must be acknowledged. In contrast to the preceding study, which could not approve the reliability of the trial because the active comparator was not superior to placebo, the reliability of this trial was shown as citalopram was superior to placebo in the present study.

The percentage of patients rated as responders was significantly higher in the active groups (55.0% hypericum extract, 56.7% citalopram) than in the placebo group (39.2%, p = 0.0026 and p = 0.0006, respectively). When comparing response rates with the results of other hypericum studies with chemically defined antidepressants as comparative drug, the response rates are comparable; they range normally between 50 and 70% after 6 weeks of treatment [20,33,42]. In a meta-analysis of placebo rates in major depressive disorder trials with chemically defined antidepressants, placebo response rates were 45.5% (PP) and 26.9% (ITT) [39]. Within psychiatry, and more specifically, regarding the affective disorders, responses to the use of placebo have been more frequently described and the rates recorded go from 20 to 49% [23]. Khan et al. [17] found that only 21.1% of antidepressant treatment arms in trials with high placebo response (> 30% mean change from baseline) showed statistical superiority over placebo compared with 74.2% in trials with a low placebo response (≤ 30).

Concerning tolerability and safety of treatment, hypericum revealed a favourable safety profile in comparison to citalopram. No patient in the hypericum group had an assessment of tolerability that was rated either "moderate" or "poor" on day 42 of treatment. In the present study, a total of 222 adverse events were documented for 138 (35.6%) patients. In the investigator assessments of the relationship of the AEs to the study medication, a significant lower rate of "certain", "probable" or "possible" relationships was observed in the hypericum group (17.2%) than in the citalopram group (53.2%). In the Placebo group 30% related AEs occurred. A much lower number of AEs with certain relation to study medication was observed in the hypericum group (3.4%) and the placebo group (5.7%) than in the citalopram group (10.6%).

This evaluation confirms the results of previous studies, that hypericum is a safe preparation with a rate of side effects not higher than placebo. According to observational studies with preparations of St. John's Wort, an incidence of adverse events (AE) between 1 and 3% among those treated was recorded. This is some ten times less than with synthetic antidepressants. The most common adverse events (1 per 300 000 treated cases) among the spontaneous reports in the official register, concern reactions of the skin exposed to light [35]. In addition, interactions with various drugs, most likely related to the induction of cytochrome P450 isoenzymes (especially CYP3A4) and/or P-glycoprotein were reported. Therefore, it was suggested that long-term administration of St. John's wort may result in diminished clinical effectiveness or increased dosage requirements for all CYP3A4 substrates such as ciclosporin A, indinavir, digoxin, warfarin and others [21].

For citalopram, well-designed short- and long-term trials demonstrate an overall safety/side effect profile consistent with other SSRIs. The more frequent adverse events (nausea, somnolence, dry mouth, increased sweating) are mainly transient, mostly mild to moderate in severity, and observed consistently across studies at rates similar to other SSRIs. Citalopram treatment did not increase risk of suicide, overdose, seizure, or arrhythmia [25]. In the study of Hovorka et al. [10] nausea was the most common adverse event of citalopram in 7 patients (16.3%) during the first month of treatment and in 3 patients (6.9%) during the second month of treatment. Sexual dysfunction (decrease of libido) was reported in 2 (4.7%) male patients during the entire course of treatment.

This study also confirmed, that the long half-life times of the most important active constituents of hypericum extracts allow a once-daily dosage regimen resulting in better patient compliance. Similar results for antidepressants [44] as well as for hypericum extracts [2,7,29] were reported recently. For Laif 900®, the following half-life times were determined: hypericin 18.7 ±4.8 h, pseudohypericin 17.2 ±8.4 h and hyperforin 17.5 ±4.5 h [32]. This is in accordance with the recommended once-daily use of other antidepressants having half-lives up to 24 hours such as citalopram.

It can be concluded that the present study confirms previous data in respect of safety and tolerability of hypericum extract. The incidence and character of adverse effects observed with citalopram was in the range reported from other studies as well as the placebo-response observed in this study.

The results of the study demonstrate for the first time the non-inferiority of hypericum extract STW3-VI in comparison to the SSRI citalopram in the treatment of moderate depression with a once-a-day dosage. Citalopram was shown to be as effective as older classical antidepressants in the treatment of moderate depression, while less adverse effects occurred in comparison to tricyclic and tetracyclic antidepressants. Despite this, the occurrence of the remaining side-effects due to treatment with citalopram results in a low patient compliance. Thus, the demonstrated efficacy and good tolerability make hypericum extract STW3-VI a drug of consideration in the treatment of outpatients with moderate depression and a valuable alternative to modern chemically defined antidepressants.

Conclusions

In this double-blind, randomised, multicentre study comparing a once-daily dosage of hypericum extract STW3-VI versus the SSRI citalopram and versus placebo over 6 weeks, therapeutic efficacy and tolerability of hypericum extract STW3-VI could be demonstrated. One of the main advantages is the once-daily dosage which facilitates compliance. The clinical study proved clearly that hypericum extract is not inferior to citalopram and that both drugs are effective in the treatment of moderate depression and superior to placebo as judged by HAMD scores and scores on other rating scales. Thus, the available study confirms the results of preceding studies with hypericum extract and other chemically defined antidepressants. In addition, the favourable safety and tolerability of hypericum extract STW3-VI in comparison to citalopram was demonstrated. The demonstrated equivalent efficacy

to citalopram in antidepressive therapy and the excellent tolerability revealed that hypericum extract STW3-VI is a good alternative to chemically defined antidepressants in the treatment of outpatients with moderate depression.

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