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Rhodiola rosea in Subjects with Prolonged or Chronic Fatigue Symptoms: Results of an Open-Label Clinical Trial

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Keywords
Chronic fatigue · Clinical trial · Prolonged fatigue · *Rhodiola rosea* · Rosalin · WS® 1375

Summary
Background: *Rhodiola rosea* roots and rhizomes are a herbal medicine for temporary relief of stress symptoms such as fatigue and sensed weakness. A daily dosage of 400 mg is recommended. **Methods:** A dry ethanolic extract of *R. rosea* (WS® 1375) was studied in 100 subjects with prolonged or chronic fatigue symptoms. In an uncontrolled, open-label multicenter clinical trial, the subjects were administered 2 × 200 mg WS® 1375 over 8 weeks. Outcome measures were scales and tests related to fatigue. They were evaluated in an exploratory data analysis to generate hypotheses regarding efficacy. The pilot character of the trial is marked by its broad focus on subjects suffering from fatigue in general and by its comparatively long duration. **Results:** The greatest change was observed after 1 week of treatment. The fatigue symptoms continued to decline further, with statistically significant improvement at week 8. The safety assessments of WS® 1375 during the trial proved to be favorable, with most adverse events being of mild intensity and not related to the study drug. **Conclusions:** The results indicate that 2 × 200 mg WS® 1375 may be an effective treatment in subjects suffering from prolonged or chronic fatigue. The safety and tolerability of WS® 1375 also presented a favorable profile.

Schlüsselwörter
Chronische Erschöpfung · Klinische Studie · Andauernde Erschöpfung · *Rhodiola rosea* · Rosalin · WS® 1375

Zusammenfassung
Hintergrund: Die Wurzeln und Rhizome von *Rhodiola rosea* werden als Heilpflanze zur vorübergehenden Linderung von Stresssymptomen wie Erschöpfung oder Schwächegefühl eingesetzt. Die empfohlene Tagesdosis liegt bei 400 mg. **Methoden:** Das Studienmedikament, ein ethanolischer Trockenextrakt aus *R. rosea* (WS® 1375), wurde bei 100 Patienten mit Symptomen andauernder oder chronischer Erschöpfung angewendet. Den Teilnehmern wurde im Rahmen einer unkontrollierten, offenen, multizentrischen klinischen Studie über die Dauer von 8 Wochen eine Tagesdosis von 2 × 200 mg WS® 1375 verabreicht. Messgrößen waren erschöpfungsbezogene Skalen und Tests, die auf exploratorischer Ebene hinsichtlich der Wirksamkeit von WS® 1375 ausgewertet wurden. Der breite, auf Fatigue-Patienten im Allgemeinen ausgerichtete Fokus sowie die vergleichsweise lang angesetzte Dauer kennzeichnen den Pilotcharakter der Studie. **Ergebnisse:** Die größten Veränderungen der Analysewerte wurden nach 1 Woche Behandlungsdauer gemessen. Die Erschöpfungssymptome gingen danach weiter zurück und hatten sich bis Woche 8 statistisch signifikant verbessert. Die Sicherheitsbewertung von WS® 1375 während der Studie fiel günstig aus, da die meisten unerwünschten Ereignisse von milder Ausprägung und nicht dem Studienmedikament zuzuordnen waren. **Schlussfolgerungen:** Die Resultate lassen auf einen Behandlungseffekt von 2 × 200 mg WS® 1375 bei Patienten mit andauernder oder chronischer Erschöpfung schließen. Günstige Ergebnisse zeigten sich auch in Bezug auf die Sicherheit und Verträglichkeit von WS® 1375.

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Introduction

Fatigue is commonly defined as a feeling of tiredness, lack of energy, emotional stability and motivation, or difficulty in concentration and memory [1, 2]. The clinical course is frequently aggravated by a variety of attending symptoms such as headache or muscle pain. Applicable duration categories are: recent fatigue: < 1 month; prolonged fatigue: 1–6 months; chronic fatigue: > 6 months [2, 3].

While earlier data suggest the prevalence of the chronic fatigue syndrome (CFS) to be at about 0.04% or even less [4], a recent study from The Netherlands shows that approximately 1% of the adult population reported complaints that correspond to chronic fatigue symptoms according to the Center of Disease Control (CDC) criteria [5]. This study and other recent studies [5–8] state that up to one-third of the adult population has experienced fatigue symptoms not fully meeting the CDC criteria. These recent findings suggest that chronic fatigue and related symptoms might be more common than previously thought.

The considerable number of chronic fatigue-related symptoms expected to exist among the adult population, as well as the unfavorable condition that no standard medication is as yet available [4, 9], encouraged us to conduct a trial on the effects of *Rhodiola rosea* in patients who had experienced fatigue over a period of at least 2 months and who thus would form a cohort representing fatigue without further specifications. As chronic fatigue is likely to result from a prolonged lack of fatigue treatment [10], the identification of an efficient and safe fatigue therapy, also in rather mild or prolonged, not yet chronic cases, was regarded to be even more warranted.

Given the probability of multiple etiologies for prolonged or chronic fatigue, a promising approach towards a successful therapy is offered by the concept of adaptogens, which refers to substances traditionally applied to improve mental and physical performance. Adaptogens are considered to be nearly non-toxic and of non-specific effect, thus being capable of generally strengthening the organism against adverse factors like stress [11]. Stress is considered a major possible precondition for the onset of fatigue [12–14].

R. rosea is reported to have adaptogenic properties [15–17]. The root stock contains 6 distinct groups of active compounds, among which the phenylpropanoids rosavin and rosarin are considered to occur only in *R. rosea* [18, 19]. Due to its adaptogenic features, *R. rosea* belongs to those herbal medicines that are reported to improve mental performance and enhance endurance in fatigue [20]. The recommended daily dosage of *R. rosea* is 400 mg [21].

Recent studies have demonstrated that *R. rosea* can reduce mental fatigue under stressful conditions [22–24] or conditions of ongoing life-stress symptoms [25]. A controlled trial showed the superiority of *R. rosea* over placebo in improving mental fatigue as measured by the Pines burnout scale [26]. Furthermore, results from animal studies suggest a stimulating effect of *R. rosea* on the physical work capacity [27].

As to date no standard medication is available to effectively treat presentations of fatigue [4, 9], the objective of the presented trial was to gain insights into the therapeutic effects of *R. rosea* in patients who had experienced fatigue over a period of at least 2 months. Other than most of the preceding studies which examined a specified range of fatigue patients such as night-shift workers or examinees, in this trial a narrow subject definition was abandoned in order to find results applicable to a wide range of fatigue patients. Also, the duration of the trial was comparatively longer than in most studies on *R. rosea* in fatigue patients performed to date [28].

Methods

Trial Design and Setting

The present study was conducted to evaluate the therapeutic effect, safety, and tolerability of the dry ethanolic *R. rosea* extract WS® 1375 (Rosalin; Rosalin is the active substance of Vitango®, manufactured by Dr. Willmar Schwabe GmbH & Co. KG, Germany) (drug/extract ratio 1.5–5:1). The objective of this trial was to describe the named outcomes of WS® 1375 in subjects with symptoms of prolonged and chronic fatigue. The study aimed at obtaining results applicable to as many subjects as possible suffering from fatigue.

This trial was designed as an open-label, single-arm, multicenter study. It was conducted at the Neurology Departments of 5 hospitals in Ukraine. Planning, execution, and analysis of the trial were carried out in accordance with the national regulations. The study followed the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice and the Declaration of Helsinki for Humans. In order to ensure the reliability of data obtained at the respective sites, investigators received extensive rater training by expert trainers selected by the sponsor prior to study initiation.

Trial duration was 8 weeks; the study medication was administered as 2 tablets daily, each containing 200 mg of WS® 1375.

Outcome Measures

Treatment effects were measured by changes of stress symptoms, fatigue, quality of life, mood, concentration, and general health. Safety and tolerability were monitored by comparison of physical examinations, laboratory data, and vital signs measurements between baseline and end of treatment, and by adverse event (AE) screening. The following scales were employed:

- Multidimensional Fatigue Inventory 20 (MFI-20): The MFI-20 is a validated 20-item self-report instrument designed to measure fatigue [29, 30]. It consists of 5 subscales of fatigue: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity.
- Numeric Analogue Scales (NASs) of chronic fatigue symptoms according to CDC definition: 3 self-rating NASs assessing 'postexertional malaise', 'impairment of concentration/memory', and 'nonrestorative sleep' were applied.
- Numbers Connecting Test (NCT): The NCT [31] is a language-free, timed test to assess the speed of executive function.
- Sheehan Disability Scale (SDS): The SDS is a validated 3-item self-report inventory designed to assess the degree to which symptoms of panic, anxiety, depression, or phobia have disrupted the patient's work, social life, and family life [32].
- Pittsburgh Sleep Quality Index (PSQI): The PSQI [33] is a validated self-rated questionnaire that assesses sleep quality and disturbances retrospectively over a 4-week time interval.
- Recent Perceived Stress Questionnaire (PSQ-R): The 30-item PSQ-R is a self-rating instrument to assess subjectively experienced stress [34].
- Beck Depression Inventory II (BDI-II): The BDI-II is a validated 21-item questionnaire designed to assess symptoms of depression such as sadness, guilt, loss of interest, social withdrawal, and suicidal ideation [35].
- Clinical Global Impressions (CGI): The CGI scales are widely used as validated measures of treatment outcome [36]. Ratings are recorded during an interview between investigator and patient and then evaluated by the former. In this trial, only the items 'change from baseline', 'therapeutic effi-

cacy', and 'tolerability' were employed and evaluated on the Clinical Global Impression of Change scale.

All outcome measures, except the CGI, were assessed right after the patient had been enrolled in the study and before the first dose of study medication was administered. The patients were asked to return for follow-up visits after 1, 4, and 8 weeks.

The outcome measures of the MFI-20, NASs, NCT, SDS, and CGI were collected at weeks 1, 4, and 8. The PSQI, PSQ-R, and BDI-II results were collected at weeks 4 and 8.

Self-rating scales were completed by the participants at the predefined times. All other scales were assessed by the investigator at the respective study site.

Safety Measures

In addition to the efficacy results, safety outcome variables were assessed at baseline and at week 8 or at an early termination visit, including physical examination, vital signs, 12-lead electrocardiography (ECG), and laboratory tests. All AEs were recorded in AE report forms by the respective investigator.

Participants

It was planned to recruit 100 male and female outpatients aged 18–60 years with prolonged or chronic fatigue symptoms.

The following inclusion criteria had to be met:

- Clinically evaluated, unexplained persistent or relapsing fatigue symptoms lasting for at least 2 months that were not the result of ongoing exertion, not substantially relieved by rest, and leading to substantial reduction in previous levels of occupational, educational, social, or personal activities.
- Chronic fatigue symptoms assessed as ≥ 5 on the NASs for 'postexertional malaise lasting more than 24 hours', 'substantial impairment in short-time memory and concentration', and 'unrefreshing sleep'.
- MFI-20 score ≥ 7 for the subscales 'general fatigue', 'physical fatigue', 'mental fatigue'.
- Sufficient language skills, readiness and ability to comply with the physician's instructions, to respond to all interview questions and to fill in the self-assessment scales without evident difficulties and without the assistance of an interpreter.

Exclusion criteria were:

- Participation in another drug trial; current hospitalization; BDI-II item 9 ≥ 1; history/evidence of substance abuse or dependence within the last 5 years; history of Axis I disorders according to the Diagnostic and Statistic Manual of Mental Disorders (DSM)-IV at least 1 year before enrolment; nonmedical psychiatric treatment at least 4 weeks before the study; unacceptability to discontinue or likelihood to need any psychotropic drugs, clinically significant abnormality of ECG or laboratory values, cardiovascular diseases, respiratory diseases, metabolic disorders or progressive diseases, cerebrovascular and neurologic diseases, any acute, latent, or chronic form of infection; gastrointestinal disorders with uncertain absorption of orally administered drugs; pregnancy or lactation and known hypersensitivity to *R. rosea* extract, insufficient contraception in pre-menopausal women.

Baseline Examinations

Medical history and concomitant diseases/medication were assessed at the screening visit (day –2). Also, a physical examination was performed by a physician at the screening visit and at study termination (week 8). Further examinations performed at baseline (day 0) were a 12-lead ECG, standard laboratory tests of blood samples (hematology, metabolites, liver enzymes, coagulation parameters, and electrolytes), and urine analysis using urine sticks for the presence of proteins, blood, and glucose. The screening visit included a first completion of all questionnaires involved, except for the CGI.

Signed informed consent according to ICH regulations was obtained at the screening visit. The overall examination of subjects at the screening visit, medical history anamnesis, and physical and neurological examination were performed by a physician in accordance with standard procedures at the investigation site. Hematology and clinical chemistry tests were done by 1 central laboratory.

Intervention

Treatment started on the morning of day 1. Patients were asked to take one 200-mg tablet before breakfast and one before lunch, with a glass of water.

Statistical Methods

Since this study was an open-label exploratory trial, no hypotheses were formulated and the data were analyzed to be reported descriptively.

In order to investigate the therapeutic effects of WS® 1375 in subjects with symptoms of prolonged or chronic fatigue during 8 weeks of treatment, the absolute and relative intra-individual changes of the outcome parameters between baseline and end of treatment were evaluated. Also, time courses of the outcome parameters were analyzed. Descriptive statistics were computed to describe the empirical distributions; 95% confidence intervals (CIs) for the expected values and medians were calculated. Accordingly, the resulting p-values (2-sided p-values of the Wilcoxon signed-rank test) and the phrase 'statistical significance' have to be interpreted in an exploratory sense.

Analysis was primarily based on the full analysis set (FAS) including all subjects having received the study drug at least once and having had at least 1 measurement of one of the rating scales during the treatment period. Missing values of some items or total scores during the treatment period were replaced by the last observation carried forward (LOCF) method.

Due to the exploratory character, no adjustments for multiplicity were applied and no formal estimation of sample size accounting for type I error rate, power, standard deviation (SD), and effect size was done. The definition of the sample size of 100 subjects was done based on the fact that analyzing 100 datasets results in an 80% power to detect a minimum standardized difference of 0.5 within a 1-group multivariate repeated measures design for a 2-sided test, 4 time points, and a descriptive significance level $\alpha = 0.05$ [37].

The case report form (CRF) data were double-entered into the database by independent, trained personnel. The system used for this purpose was the validated Clinical Trial Management System 'Clincase Software 2.6'. Statistical analyses were performed using SAS® version 9.2 (SAS, Cary, NC, USA).

Results

Demographic Characteristics at Baseline

In total, 112 subjects were screened for inclusion. Each center recruited between 8 and 27 subjects. 11 of the screened subjects were not included into the treatment phase due to screening failure, without any intake of the investigational product. The remaining 101 subjects were enrolled and received the investigational treatment at least once. During the treatment phase, 1 subject terminated the study prematurely due to violation of the exclusion criteria. The FAS therefore comprised 100 subjects, 31 male, 69 female ones. The mean age was 37.8 ± 9.5 years; the mean weight was 72.1 ± 13.5 kg. The first subject was included in December 2011; the last visit of the last patient was conducted in May 2012.

Outcome Measures

All outcome measures are presented with regard to the FAS.

The evaluation of the MFI-20 assessments reveals a significant improvement in all subscales ($p < 0.0001$). The greatest change was found for the subscale 'general fatigue' with a difference to baseline of 8.2 ± 4.1 points at week 8. For the subscales 'physical fatigue', 'mental fatigue', 'reduced activity', and 'reduced motivation', change values of 6.9 ± 4.4, 6.0 ± 3.9, 6.5 ± 4.3, and 3.3 ± 3.3, respectively, were found at the end of treatment. In all MFI-20 subscales, the most pronounced change occurred in the course of week 1. Improvement continued up to the end of the trial (fig. 1).

On all NASs for chronic fatigue symptoms according to CDC, significant improvements between the screening visit and the following visits were found ($p < 0.0001$). The degrees of improvement were similar among the different scales (fig. 2).

Significant improvement was also demonstrated for most values assessed by the SDS in week 8 compared to baseline. The outcome measures for 'impairment at work', 'impairment in social life', and 'impairment in family life' improved considerably (table 1).

Values measured by the NCT markedly improved in the course of the trial. The mean total score of the NCT decreased significantly from 103.4 ± 40.8 s to 85.1 ± 37.1 s with a difference of 18.4 ± 17.2 s between screening and week 8 ($p < 0.0001$).

The PSQ-R score decreased in the course of the treatment and was reduced by 0.2 ± 0.2 points at week 8 ($p < 0.0001$), which corresponds to a mean reduction of the total stress score by 41.8%. Among the PSQ-R subscores, the 'fatigue' value had decreased by 38.8% at week 8 and was thus the PSQ-R subscore with the greatest improvement ($p < 0.0001$) (table 2).

The mean PSQI total score decreased from 8.0 ± 3.1 to 4.8 ± 2.5 between screening and week 4 and continued to decrease further, resulting in an average PSQI total score of 3.7 ± 2.2 after 8 weeks of treatment. Both differences were statistically significant ($p < 0.0001$ both). Similar to the total score, all subscores of the PSQI decreased significantly from week 4 onwards.

The mean total score of the BDI-II improved from a screening score of 10.8 ± 5.0 to 5.6 ± 4.5 and 4.0 ± 4.3 at week 4 and week 8, respectively ($p < 0.0001$ each).

With regard to the CGI global improvement, 83/100 (83.0%) subjects reported 'very much' or 'much' improved conditions at

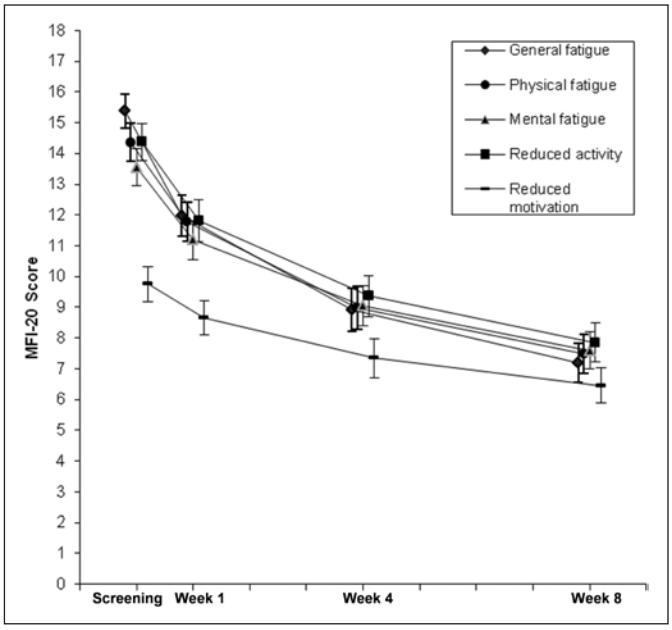

Fig. 1. Multidimensional Fatigue Inventory 20 (MFI-20): Time course of single items between screening and week 8 (mean and 95% CI, FAS, n = 100, LOCF).

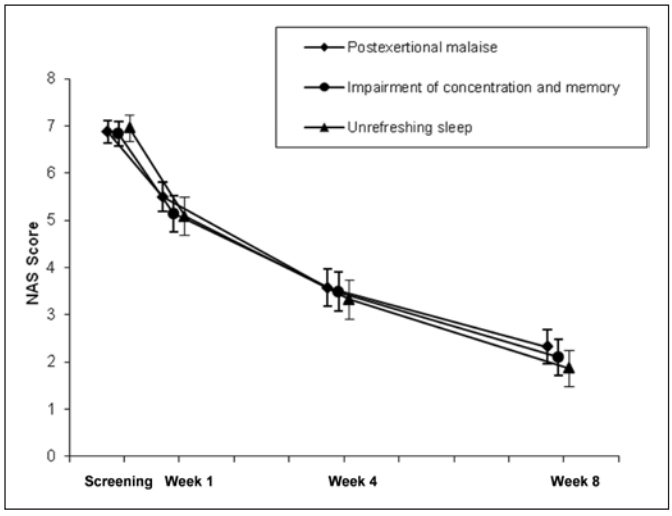

Fig. 2. Three Numerical Analogue Scales (NASs) of chronic fatigue symptoms: Time course of single items between screening and week 8 (mean and 95% CI, FAS, n = 100, LOCF).

Table 1. Sheehan Disability Scale (SDS): time course of total score and single items

Item	Screening	Week 1	Week 4	Week 8	Difference (week 8/screening)	p-Value*
Total score (global impairment)	17.0 ± 5.0, 17.5 [16.0; 18.0][a]	13.2 ± 5.2, 14.0 [12.0; 15.0]	8.6 ± 5.1, 9.0 [7.0; 10.0]	4.7 ± 4.3, 4.0 [3.0; 5.0]	–12.3 ± 6.3, –13.0 [–14.0; –11.0]	< 0.0001
Impairment work/ school	5.7 ± 2.0, 6.0 [5.0; 6.0]	4.6 ± 1.9, 5.0 [5.0; 5.0]	3.0 ± 1.9, 3.00 [2.0; 3.0]	1.7 ± 1.5, 1.0 [1.0; 2.0]	–4.0 ± 2.3, –4.0 [–5.0; –3.0]	< 0.0001
Impairment social life	5.4 ± 2.1, 6.0 [5.0; 6.0]	4.1 ± 2.0, 4.0 [4.0; 5.0]	2.8 ± 1.8, 3.0 [2.0; 3.0]	1.5 ± 1.4, 1.0 [1.0; 1.0]	–3.9 ± 2.6, –4.0 [–5.0; –4.0]	< 0.0001
Family life/home responsibilities	5.9 ± 2.0, 6.0 [5.0; 7.0]	4.4 ± 2.0, 5.0 [4.0; 5.0]	2.8 ± 1.8, 3.0 [2.0; 3.0]	1.5 ± 1.5, 1.0 [1.0; 2.0]	–4.4 ± 2.3, –5.0 [–5.0; –4.0]	< 0.0001
Days lost	0.5 ± 0.9, 0.0 [0.0; 0.0]	0.2 ± 0.6, 0.0 [0.0; 0.0]	0.1 ± 0.5, 0.0 [0.0; 0.0]	0.1 ± 0.5, 0.0 [0.0; 0.0]	–0.4 ± 0.8, 0.0 [0.0; 0.0]	< 0.0001
Days underproductive	2.5 ± 1.7, 2.0 [2.0; 3.0]	1.6 ± 1.6, 1.0 [0.0; 1.0]	1.0 ± 1.3, 0.0 [0.0; 0.0]	0.7 ± 1.2, 0.0 [0.0; 0.0]	–1.8 ± 1.8, –2.0 [–2.0; –1.0]	< 0.0001

[a]Mean ± SD, median [95% CI].
*p-Value of the 2-sided Wilcoxon signed-rank test, FAS, n = 100, LOCF. The p-value refers to 'Difference (week 8/screening)'.
SD = Standard deviation; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward.

Table 2. Recent Perceived Stress Questionnaire (PSQ-R): time course of total score and single items

Item	Screening	Week 4	Week 8	Difference (week 8/screening)	p-Value*
PSQ-R stress score	0.6 ± 0.1, 0.6 [0.5; 0.6][a]	0.4 ± 0.1, 0.4 [0.3; 0.4]	0.3 ± 0.1, 0.3 [0.3; 0.4]	−0.2 ± 0.2, −0.2 [−0.3; −0.2]	< 0.0001
Subscales					
Harassment	9.2 ± 2.2, 9.0 [9.0; 10.0]	8.1 ± 2.1, 8.0 [8.0; 9.0]	7.3 ± 2.1, 7.0 [6.0; 8.0]	−1.9 ± 2.2, −2.0 [−2.0; −1.0]	< 0.0001
Overload	11.9 ± 2.3, 12.0 [12.0; 13.0]	10.9 ± 2.3, 11.0 [11.0; 12.0]	10.4 ± 2.2, 10.0 [10.0; 11.0]	−1.5 ± 2.3, −1.0 [−2.0; −1.0]	< 0.0001
Irritability	5.7 ± 1.2, 6.0 [5.0; 6.0]	4.3 ± 1.4, 4.0 [4.0; 5.0]	3.8 ± 1.3, 4.0 [4.0; 4.0]	−1.9 ± 1.6, −2.0 [−2.0; −1.0]	< 0.0001
Lack of joy	18.2 ± 3.2, 18.0 [17.0; 19.0]	14.9 ± 3.4, 15.0 [14.0; 16.0]	13.9 ± 3.5, 14.0 [13.0; 15.0]	−4.4 ± 3.6, −4.0 [−5.0; −3.0]	< 0.0001
Fatigue	12.2 ± 1.7, 12.0 [12.0; 13.0]	8.4 ± 2.2, 8.0 [8.0; 9.0]	7.4 ± 2.2, 7.0 [6.0; 8.0]	−4.8 ± 2.5, −5.0 [−6.0; −4.0]	< 0.0001
Worries	12.5 ± 2.7, 12.0 [11.0; 13.0]	9.9 ± 2.3, 10.0 [9.0; 10.0]	9.0 ± 2.3, 9.0 [8.0; 10.0]	−3.4 ± 2.8, −3.0 [−4.0; −3.0]	< 0.0001
Tension	10.7 ± 2.1, 11.0 [10.0; 12.0]	7.8 ± 2.1, 8.0 [7.0; 8.0]	7.0 ± 2.0, 7.0 [6.0; 7.0]	−3.8 ± 2.8, −4.0 [−5.0; −3.0]	< 0.0001

[a]Mean ± SD, median [95% CI].
*p-Value of the 2-sided Wilcoxon signed-rank test, FAS, n = 100, LOCF. The p-value refers to 'Difference (week 8/screening)'.
SD = Standard deviation; CI = confidence interval; FAS = full analysis set; LOCF = last observation carried forward.

week 8. This also applies to the CGI therapeutic effect with a 'marked' or 'moderate' improvement in 84% of the trial participants at week 8.

Safety

During the active treatment and the subsequent risk phase, 41/101 (40.6%) subjects experienced a total of 44 AEs, leading to an overall incidence rate of 0.007 AEs/day of exposure. Most of the AEs (32/44 (72.7%)) were assessed as 'not related' to the study drug. For 12/44 AEs (27.3%) a causal relationship with the study drug could not be excluded but was assessed as 'unlikely' in all cases. In most of the cases, the intensity of the AE was mild (36/44 (81.8%)), otherwise moderate (8/44 (18.2%)). None of the patients terminated the study prematurely because of AEs. The largest number of AEs referred to nervous system disorders and the gastrointestinal system, which corresponds to the study indication. One serious AE (SAE) occurred with a patient being hospitalized due to community-acquired pneumonia, which was assessed as not related to the study drug. None of the laboratory parameters presented a considerable mean change during the course of the study. No clinically relevant deviations in the 12-lead ECG and vital signs measurements at screening and week 8 were observed. A summary of the AE monitoring during the study is given in table 3.

Compliance

Compliance assessment was based on unused investigational product returned at the week 1, week 4 and week 8 (termination) visits. A deviation concerning compliance was considered as relevant if the calculated compliance was < 80% or > 120%. None of the subjects had to be excluded due to lack of investigational product compliance.

Table 3. AEs during active treatment and the 1-week risk phase

AE (MedDRA system organ class)	Number of patients[a]
Any patients with AE(s)	41
Cardiac disorders	2
Gastrointestinal disorders	8
General disorders and administration site conditions	4
Hepatobiliary disorders	1
Infections and infestations	7
Investigations	1
Metabolism and nutrition disorders	1
Musculoskeletal and connective tissue disorders	3
Nervous disorders	9
Psychiatric disorders	3
Renal and urinary disorders	1
Reproductive system and breast disorders	2
Respiratory, thoracic and mediastinal disorders	2

[a]Absolute frequency, safety analysis set (SAF), n = 101.
AE = Adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Discussion

The values of nearly all outcome variables improved markedly over time, with none of them increasing. While a substantial alleviation of symptoms could already be observed after the first week of treatment, the symptoms continued to decline until the final evaluation at week 8.

The MFI-20 analysis shows significant improvement in all subscales over the duration of the treatment, with the most marked changes in the subscale 'general fatigue'. A less pronounced impact

was observed for the subscale 'reduced motivation', which, however, may be explained by the relatively low baseline values.

The evaluation of results assessed by the NASs for chronic fatigue symptoms according to CDC revealed a significant improvement between the screening visit and the following visits. The degrees of improvement were similar among the different scales and suggest an overall beneficial effect of *R. rosea* on the capability to recover from mental or physical stress (items 'postexertional malaise' and 'unrefreshing sleep'), as well as on mental performance (item 'impairment of memory and concentration') (fig. 2). These findings indicate a therapeutic effect of WS® 1375 on chronic fatigue-related symptoms. A broad application range in conditions of fatigue and a possible inhibition of the development of chronic fatigue from minor fatigue presentations through *R. rosea* administration are thus suggested. The findings are in line with publications reporting the beneficial effect of *R. rosea* on physical and mental performance [22–24] and are further supported by the favorable results achieved for the NCT in this trial.

The impairments regarding everyday activities and normal functioning that are imposed upon patients by fatigue conditions were measured by means of the SDS. Significant improvement was demonstrated for most values assessed in week 8 compared to baseline. Like the 'global impairment' score, also the outcome measures for the subscores 'impairment at work', 'impairment in social life', and 'impairment in family life' improved considerably (table 2), thus suggesting a beneficial impact on quality of life through improved fatigue symptoms.

The screening score index of the PSQ-R indicates significant preexisting perceived stress in our study population, since this value corresponds to the upper quartile according to the validation study by Levenstein et al. [34]. The results obtained in this trial show that until week 8 the score index decreased, finally reaching the second quartile. This is a statistically significant and clinically relevant alleviation of stress symptoms, in which 'fatigue' was found to be the subscore with the highest improvement values among the PSQ-R values assessed (table 2).

The analysis of the BDI-II revealed a rather low mean total score at screening (10.8 ± 5.0), which indicates only minimal depression in our study population. Still, the mean total score of the BDI-II significantly decreased at weeks 4 and 8, which suggests a beneficial effect of WS® 1375 on the symptoms of depression in patients suffering from prolonged or chronic fatigue. This finding supports the results obtained by Olsson et al. [26], who reported a marked beneficial effect of *R. rosea* on both fatigue- and depression-related symptoms as measured by the Pines burnout scale and the Montgomery-Asberg depression rating scale (MADRS), respectively.

The results of the CGI scales also indicate considerable efficacy ratings for WS® 1375 in the treatment of fatigue and thus correspond to the results of the patient-rated assessments described above. According to the CGI rating, the vast majority of the trial participants experienced a marked improvement of their fatigue symptoms after 8 weeks of treatment with 2 × 200 mg WS® 1375 as compared to baseline. Similar results were obtained regarding the therapeutic effect of the *R. rosea* extract.

The consistent results obtained in this trial were also confirmed by analyses of repeated measurements. Our findings indicate that the favorable impact of WS® 1375 in patients suffering from prolonged or chronic fatigue was not restricted to core fatigue symptoms such as physical fatigue, mental fatigue, reduced activity, or prolonged exhaustion, as evaluated by the MFI-20 and the respective NASs. The marked improvement also encompassed many of the attending symptoms like depression (BDI-II), reduced sleep quality (PSQI), subjectively experienced stress (PSQ-R), and impaired executive function (NCT). These single aspects also translated into an improved overall outcome and positive impact on many aspects of everyday life, as indicated by the improvement in the CGI and SDS scales. Our results thus confirm published findings from research on the adaptogenic properties [15–17] and related therapeutic effects of *R. rosea* [22–26] and prove the applicability of these findings to the target group studied in this trial. The patients in this study showed only overlapping low levels of depressive symptoms with a low initial BDI-II score. Nevertheless, the BDI-II score decreased even further during the course of the study treatment.

WS® 1375 presented a favorable safety profile. Most of the AEs were of mild intensity and not or not likely to be related to treatment. Given the favorable results of the efficacy and safety assessments obtained over the 8-week course of the study presented here, this trial marks an important step towards the future long-term testing of efficacy and tolerability of *R rosea* in fatigue patients.

Shortcomings

Due to the exploratory character of the trial, no adjustments for multiplicity were made. Nevertheless, while exploratory analyses cannot claim to be confirmatory, they do allow the revelation of trends if applicable and the generation of hypotheses for future research. Also, these types of studies explore the usefulness for the targeted indication and provide bases for confirmatory study design, endpoints and methodologies [38].

Another limitation of this trial is the lack of a control. Notable in this context is a work by Cho et al. [39] who conducted a systematic review and meta-analysis of the placebo response in CFS. The result showed a pooled placebo response of 19.6% (95% CI 15.4–23.7%), which was thus significantly lower than expected. However, as the patients of the present study were suffering from prolonged or chronic fatigue but not from CFS, this finding may be only partly applicable. Even though the literature provides quite a few reports on clinical trials suggesting the possible success of treating fatigue symptoms with antidepressants [40], medical therapies have to date only played a minor role in the treatment of CFS and fatigue symptoms in general, which instead tend to be treated with exercise therapy or cognitive behavioral therapy [41].

The consistent results regarding the effects of WS® 1375 on all outcome parameters and the ongoing improvement over time are noteworthy. This encourages expectations that a long-term, placebo-controlled trial in patients with fatigue symptoms could show positive results for WS® 1375 with respect to prolonged or chronic fatigue and related symptoms.

Conclusions

In this open-label, single-arm trial the administration of 2 × 200 mg WS® 1375 over 8 weeks significantly improved prolonged or chronic fatigue symptoms. The safety and tolerability of WS® 1375 also presented a favorable profile.

Ethical Statement

We herewith confirm that the trial protocol has been approved by the Central Ethics Commission of the Ministry of Healthcare of Ukraine and meets the standards of the Declaration of Helsinki in its revised version of 1975 and its amendments of 1983, 1989, and 1996 (JAMA 1997;277:925–926).

Disclosure Statement

A.W. is employee of Dr. Willmar Schwabe GmbH & Co. KG, the sponsor of the trial. Y.L. officiated as an investigator in this trial and received remuneration accordingly. I.Z. received honoraria from Dr. Willmar Schwabe GmbH & Co. KG.

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