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Therapeutic Effects and Safety of *Rhodiola rosea* Extract WS® 1375 in Subjects with Life-stress Symptoms – Results of an Open-label Study

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The trial was conducted to investigate the therapeutic effects and safety of a 4 week treatment with *Rhodiola rosea* extract WS® 1375 in subjects with life-stress symptoms. This was a multicentre, non-randomized, open-label, single-arm trial. One hundred and one subjects were enrolled in this clinical study and received the study drug at a dose of 200 mg twice daily for 4 weeks. Assessments with seven questionnaires included Numerical Analogue Scales of Subjective Stress Symptoms, Perceived Stress Questionnaire, Multidimensional Fatigue Inventory 20, Numbers Connecting Test, Sheehan Disability Scale and Clinical Global Impressions to cover various aspects of stress symptoms and adverse events. Invariably, all tests showed clinically relevant improvements with regard to stress symptoms, disability, functional impairment and overall therapeutic effect. Improvements were observed even after 3 days of treatment, as were continuing improvements after 1 and 4 weeks. *Rhodiola rosea* extract WS® 1375 was safe and generally well tolerated. Adverse events were mostly of mild intensity and no serious adverse events were reported. *Rhodiola* extract at a dose of 200 mg twice daily for 4 weeks is safe and effective in improving life-stress symptoms to a clinically relevant degree.

Keywords: Rhodiola rosea; life-stress symptoms; therapeutic effects; WS® 1375.

INTRODUCTION

Stress is epidemic in the Western world and has a profound cumulative effect upon well-being and the health of the individual. Stress symptoms may manifest themselves psychologically as irritability, anxiety, impaired concentration, or physically as fatigue or exhaustion.

Today, one of the most enduring and topical forms of stress is occupational (work-related) stress that adversely affects an individual's psychological and physical health as well as the effectiveness of organizations. Studies in the workplace have shown that stress affects nearly 1 in 4 (22%) employees in the 27 European Union member states (Milczarek *et al*., 2009) with many citing high workload and lack of support as the main causes. Work-related stress is one of the biggest health and safety challenges faced in Europe. Studies suggest that stress is a factor in 50% to 60% of all lost working days (Milczarek *et al*., 2009). Women report the highest levels, but for both sexes stress can be a problem in all sectors and at all levels of an organization. Long-term work stress exerts a substantial health toll, accounting for an estimated 16% of male and 22% of female cardiovascular disease in the EU (Houtman, 2005). Stress has also been identified as a factor in the development of affective disorders such as depression (Thomas *et al*., 2007).

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Rhodiola rosea is an adaptogen considered to increase the body's resistance to stress, trauma, anxiety, exhaustion and fatigue. It appears to exert its adaptogenic effects by centrally and peripherally affecting monoamine and opioid synthesis (Stancheva and Mosharrof, 1987; Kelly, 2001), transport and receptor activity which are modified by the hypothalamic–pituitary–adrenal system (Stancheva and Mosharrof, 1987; Kelly, 2001; Brown *et al*., 2002) and furthermore revealed an antioxidative potential (Bolshakova *et al*., 1998).

In a number of clinical studies, a *Rhodiola* extract has been shown to improve mental work capacity (Saratikov *et al*., 1968; Darbinyan *et al*., 2000; Shevtsov *et al*., 2003), physical work capacity (De Bock *et al*., 2004), physical and mental capacity during stress (Spasov *et al*., 2000), symptoms of depression (Darbinyan *et al*., 2007) and mental performance in subjects with burnout and fatigue syndrome (Olsson *et al*., 2009). Clinical effects and good tolerability were observed at daily *Rhodiola* extract doses of 340–680 mg with treatment durations of up to 42 days.

This article reports the results of a 4 week treatment with *Rhodiola rosea* extract WS® 1375 (the active substance of Vitango®, Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany) in subjects with life-stress symptoms.

MATERIALS AND METHODS

Study design. This was a multicentre, non-randomized, open-label, single-arm study conducted in 13 centres in the United Kingdom. The aim of the trial was to investigate the therapeutic effects, safety and tolerability of a 4 week

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treatment with *Rhodiola rosea* extract WS® 1375 at a dose of 200 mg twice daily in subjects with life-stress symptoms. All investigators were experienced in dealing with subjects suffering from stress. Assessments were made at the beginning of treatment, after 3 days, 1 week and 4 weeks.

Subjects. Ambulatory subjects between 30 and 60 years of age with life-stress symptoms were included in the study. They had to have at least three of seven perceived life-stress symptoms assessed as ≥5 on numerical analogue scales comprising somatic symptoms, loss of zest for life, exhaustion, irritability, impairment of concentration, feeling of heteronomy and anxiety. In addition, subjects had to score ≥7 on at least one subscale of the Multidimensional Fatigue Inventory 20 (MFI-20). Subjects were excluded from study participation in the case of risk of suicide; alcohol or drug abuse or dependence; Axis I disorders according to the Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV); long-term prophylactic psychiatric treatment; non-medical psychiatric treatment; concomitant treatment with any psychotropic drugs; treatments for neuro-degenerative diseases; centrally acting antihypertensive medication; beta-blockers (exception: stable dosage for at least 4 weeks); anti-Parkinson medication; anxiolytics; muscle relaxants; analgesics of opiate type; anaesthetics; clinically significant abnormality of ECG or laboratory parameters; clinically relevant acute or chronic diseases of other organ systems; known hypersensitivity to *Rhodiola rosea* extract; pregnancy or lactation; childbearing potential without adequate contraception.

All subjects provided written informed consent. The study protocol was approved by ethics committees relevant to the study sites as well as by the Medicines and Healthcare products Regulatory Agency and was implemented in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

Study medication. All subjects were administered a 4 week treatment with film-coated tablets containing 200 mg of *Rhodiola rosea* extract WS® 1375 (Dr. Willmar Schwabe GmbH & Co. KG, Karlsruhe, Germany) and taken twice daily. 200 mg of extract (as dry extract) from *Rhodiola rosea* L. roots and rhizomes is equivalent to 300–1000 mg of *Rhodiola rosea* roots and rhizomes. The study drug was to be taken 30 min before breakfast and lunch. Compliance was assessed by pill count.

Outcomes. Outcome variables included seven Numerical Analogue Scales (NAS) of Subjective Stress Symptoms (i.e. somatic symptoms, loss of zest for life, exhaustion, irritability, impairment of concentration, feeling of heteronomy and anxiety), Perceived Stress Questionnaire (PSQ) (Levenstein *et al*., 1993), Multidimensional Fatigue Inventory 20 (MFI-20) (Smets *et al*., 1995), Numbers Connecting Test (Oswald and Roth, 1987), Sheehan Disability Scale (Sheehan *et al*., 1996; Sheehan and Sheehan, 2008), English version of the Multidimensional Mood State Questionnaire (MDMQ) (Steyer *et al*., 1997) and Clinical Global Impressions (CGI). In all tests with the exception of the MDMQ, high scores indicated severe impairment and low scores represented little impairment. Safety outcome variables included physical examination, vital signs, adverse events and laboratory tests. Due to the pilot character of the study, no primary and secondary outcome variables were defined.

Statistical analysis. Descriptive statistics were computed to describe the empirical distributions; 95% confidence intervals for the expected values and medians were calculated for the full analysis set (any subject with at least one available measurement of any rating scale) and the per protocol set (subjects of the full-analysis set without any major protocol violations). Missing efficacy values after baseline were replaced by the last-observation-carried-forward method. Descriptive testing for stress outcomes was performed using the Wilcoxon-sign test for the comparison versus baseline, so the resulting p values as well as the phrase 'statistically significant' are to be interpreted accordingly.

RESULTS

Recruitment and subject disposition

Between March and July 2009, 13 physicians screened 109 subjects with life-stress symptoms in the United Kingdom. Of these, 101 subjects were enrolled in the study and included in the safety analysis set and full analysis set according to the intention-to-treat principle (Fig. 1 for subject disposition).

Demographic characteristics at baseline

Since the analysis of the per protocol set supports the results of the full analysis set (FAS), only the results of the latter are presented in the following. At baseline, subjects in the FAS were on average 44.5 ± 7.4 years old (mean ± standard deviation) and 67.3% of the subjects were women. Mean weight was 75.9 ± 15.2 kg, mean

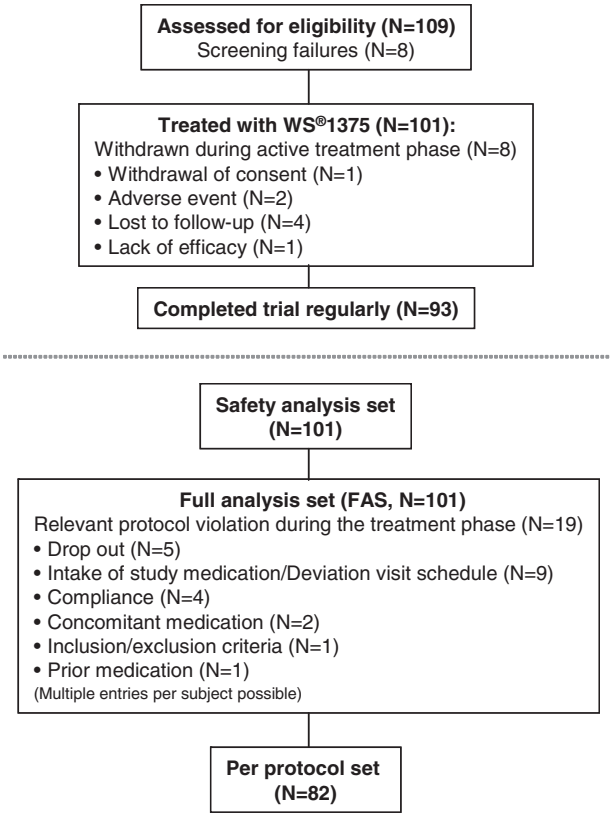

Figure 1. Subject disposition.

height 167.3 ± 9.2 cm and mean BMI 27.1 ± 5.0 kg/m^2. Table 1 summarizes these baseline characteristics.

Therapeutic effects

Numerical analogue scales. Seven subjective stress symptoms including somatic symptoms, loss of zest for life, exhaustion, irritability, impairment of concentration, feeling of heteronomy and anxiety were assessed on an analogue scale from 0 (symptom not present) to 10 (worst). Relevant mean improvement in all stress symptoms by 1.5 ± 2.5 up to 2.2 ± 2.5 points (mean ± standard deviation) was demonstrated even after 3 days of treatment. Over the course of treatment, the intensity of stress symptoms decreased further after 1 week by 2.1 ± 2.8 up to 3.2 ± 2.4 points and after 4 weeks by 2.8 ± 3.0 up to 3.7 ± 2.7 points compared with baseline (Fig. 2). All changes were statistically significant compared with baseline at any time point ($p < 0.0001$, explorative).

Perceived stress questionnaire. Assessment at the beginning and end of the study included 30 questions summarized in the seven subscales harassment, overload, irritability, lack of joy, fatigue, worries and tension. The absolute values of the subscales differ as the dimensions harassment, overload, fatigue and tension comprise four items each, the subscale irritability two items, the subscale worries five items and the subscale lack of joy seven items. Compared with baseline, mean improvements of between 1.5 ± 1.4 and 3.8 ± 4.3 points were shown for all items after 4 weeks of treatment (Fig. 3; $p < 0.0001$).

Sheehan disability scale. Functional impairment of the three inter-related domains 'work/school', 'social life' and 'family life/home responsibilities' was markedly improved even after 1 week (2.4 ± 2.3 to 2.9 ± 2.5 points) and improved further until week 4 (2.9 ± 2.7 to 3.4 ± 2.7 points compared with baseline; Fig. 4). Mean 'days lost' of the last week due to the symptoms had decreased from 0.6 ± 1.4 by 0.3 ± 1.4 days and mean 'days unproductive' of the last week from 2.4 ± 2.1 by 1.7 ± 2.0 days after 4 weeks of treatment ($p = 0.0177$ to <0.0001).

Table 1. Demographics and baseline characteristics ($n = 101$, FAS)

Gender, n (%)	
Male	33 (32.7)
Female	68 (67.3)
Age, mean ± SD (median) (years)	44.5 ± 7.4 (44.0)
Weight, mean ± SD (median) (kg)	75.9 ± 15.2 (75.0)
Mean height, mean ± SD (median) (cm)	167.3 ± 9.2 (167.0)
Body mass index, mean ± SD (median) (kg/m^2)	27.1 ± 5.0 (26.9)

Clinical global impressions. CGI Item 1 'Severity of illness' improved even after 3 days of treatment and continued to improve further after 1 and 4 weeks. All changes were statistically significant compared with baseline at any time point (data not shown). Figure 5 demonstrates changes in CGI Item 2 'Global improvement' which showed a relevant improvement in 67.1% of subjects and no change in only 12.4%. CGI Item 3.1 'Therapeutic effect' confirmed the results of CGI Item 2 with similar improvements after 4 weeks of treatment.

Multidimensional fatigue inventory 20 (MFI-20), numbers connecting test (NCT) and multidimensional mood state questionnaire (MDMQ). Improvements in MFI-20 subscales (general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation), in the speed of cognitive function according to NCT and in MDMQ dimensions (good mood – bad mood, alertness – tiredness, calmness – restlessness) were present even after 3 days of treatment with *Rhodiola rosea* extract WS® 1375 and continued to increase at 1 and 4 weeks. With the exception of 'reduced activity' in the MFI-20, all changes were statistically significant compared with baseline at any time point (data not shown).

Safety

During the treatment period, 54 adverse events were recorded in 36 subjects (35.6%; see Table 2 for details). The most common adverse events were nervous system disorders (17 [16.8%] patients with 18 [33.3%] adverse events) and gastrointestinal disorders (10 [9.9%] patients with 10 [18.5%] adverse events), which in both cases is in line with the underlying condition. Most adverse events were of mild intensity (44 [81.5%]), 10 were of moderate intensity (18.5%). No serious adverse events were reported.

Two subjects (2%) terminated the study prematurely because of adverse events (dizziness, abdominal distension). Both events were assessed to be unlikely related to the study drug.

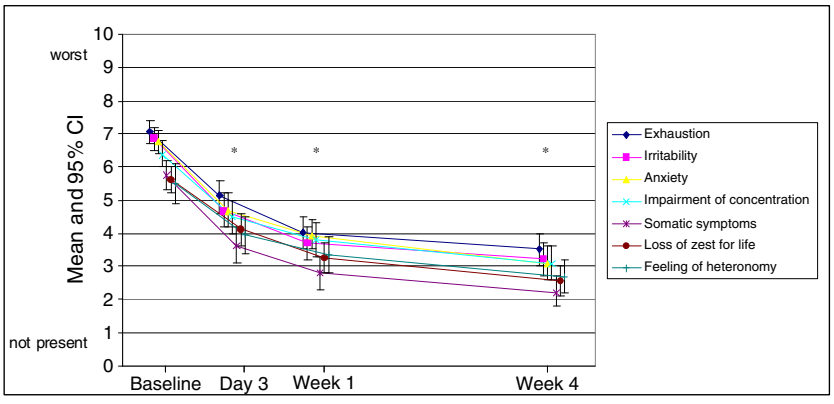

Figure 2. Numerical analogue scales over 4 weeks of treatment (n = 101**, FAS). *For all seven scales $p < 0.0001$ for the comparison with baseline. **For scales 'Impairment of concentration' and 'Feeling of heteronomy' n = 99 due to missing baseline values.

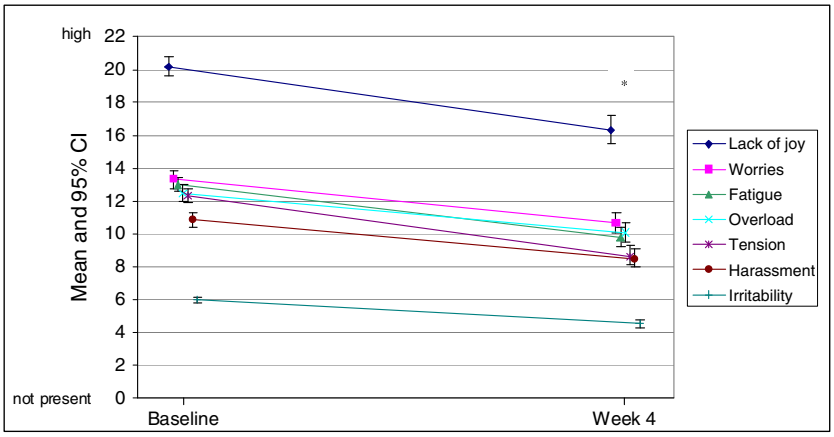

Figure 3. Perceived stress questionnaire – assessments at baseline and after 4 weeks of treatment (n = 101**, FAS). *For all seven items $p < 0.0001$ for the comparison with baseline. **For items 'Fatigue' and 'Harassment' n = 100 due to missing baseline values.

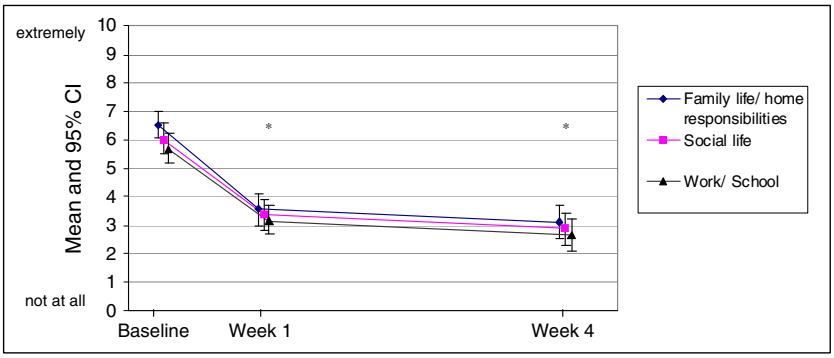

Figure 4. Sheehan disability scale – Items 'Work/School' (n = 95), 'Social life' and 'Family life/ home responsibilities' at baseline and after 1 and 4 weeks of treatment (n = 101**, FAS). *For all three items $p < 0.0001$ for the comparison with baseline. **For item 'Work/School' n = 95 due to missing baseline values.

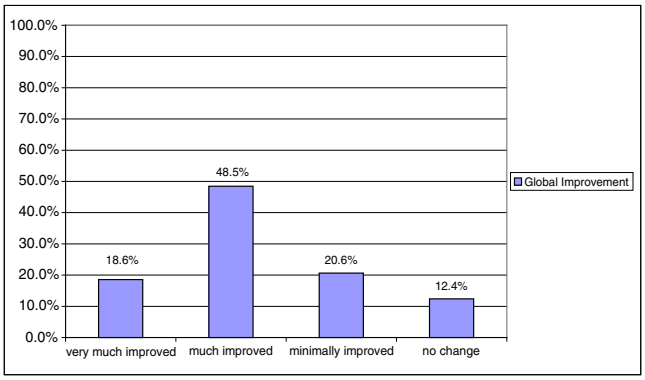

Figure 5. Clinical global impressions – CGI Item 2 'Global Improvement' after 4 weeks of treatment (n = 97, FAS).

Table 2. Adverse events (n = 101, safety analysis set)

Adverse event (MedDRA system organ class)	Number of patients (%)
Any patient with adverse events	36 (35.6)
Total number of adverse events	54
Nervous system disorders	17 (16.8)
Gastrointestinal disorders	10 (9.9)
Psychiatric disorders	5 (5.0)
Infections and infestations	3 (3.0)
Injury, poisoning and procedural complications	3 (3.0)
Respiratory, thoracic and mediastinal disorders	3 (3.0)
Investigations	2 (2.0)
Musculoskeletal and connective tissue disorders	2 (2.0)
Renal and urinary disorders	2 (2.0)
General disorders and administration site conditions	1 (1.0)
Metabolism and nutrition disorders	1 (1.0)
Reproductive system and breast disorders	1 (1.0)
Skin and subcutaneous tissue disorders	1 (1.0)

DISCUSSION

This open-label study assessed the effects of a 4 week treatment with *Rhodiola rosea* extract WS® 1375 in 101 adult subjects with life-stress symptoms. Established tests including five different subjective questionnaires to cover various aspects of stress symptoms and psychological well-being were employed. Invariably, all outcome variables showed consistent and steady improvement with regard to stress symptoms, fatigue, quality of life, mood, concentration, disability, functional impairment and overall therapeutic effect. Improvements were observed even after 3 days of treatment, as

were continuing improvements after 1 and 4 weeks. These consistent results were confirmed by subgroup analyses. In addition to the overall analysis, the efficacy variables were analysed within subgroups by gender, age, body mass index and baseline scores of PSQ, MFI-20, MDMQ and SDS (separated at the median). In total, though there were some noticeable differences between the strata in some subgroup analyses, all treatment outcome variables showed a statistically significant improvement between baseline and week 4 in all subgroups as based on the two-sided Wilcoxon signed-rank test.

Rhodiola rosea extract WS® 1375 was safe and generally well tolerated. Adverse events were mostly of mild intensity and no serious adverse events were reported.

Rhodiola rosea extract WS® 1375 belongs to a class of substances termed 'adaptogens' that are reported to have a protective effect on health against a wide variety of adverse environmental factors and emotional conditions, e.g. stress, trauma, anxiety and fatigue. The general pharmacodynamic characteristics of an adaptogenic substance are defined as follows: (1) almost non-toxic to the recipient; (2) tends to be non-specific in its pharmacological properties and acts by increasing the resistance of the organism to a broad spectrum of adverse biological, chemical and physical factors; (3) tends to be a regulator having a normalizing effect on the various organ systems of the recipient organism; (4) its effect is more pronounced the deeper the pathologic changes in the organism are (Brekhman and Dardymov, 1969).

This study confirms on the one hand the adaptogenic properties of *Rhodiola* extract with regard to non-toxicity and normalizing effects on stress conditions. On the other hand, the study confirms similar findings for *Rhodiola* extract previously reported by other authors in subjects with stress (Spasov *et al*., 2000), symptoms of depression (Darbinyan *et al*., 2007) and impaired mental performance linked with burnout and fatigue syndrome (Olsson *et al*., 2009). In these studies, *Rhodiola* extract was also well tolerated, safe and effective in improving symptoms at doses between 340 and 680 mg and treatment durations of up to 42 days.

With the parameters being analysed on an explorative level, it is important to note that the results of all psychometric tests employed point in the same direction, indicating a prompt and sustained effect of *Rhodiola rosea* extract WS® 1375.

In summary, *Rhodiola* extract WS® 1375 appears to be useful in relieving symptoms associated with life stress, such as fatigue, exhaustion and anxiety in a general practice setting.

CONCLUSIONS

This clinical study demonstrated that *Rhodiola* extract WS® 1375 at a dose of 200 mg twice daily for 4 weeks is safe and effective in improving life-stress symptoms to a clinically relevant degree in a general practice setting. The results confirm the findings and experience from previous studies on *Rhodiola rosea*.

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Conflict of Interest

D. Edwards declared no conflict of interest. A. Heufelder gave a scientific presentation for Schwabe. A. Zimmermann is an employee of Dr. Willmar Schwabe GmbH & Co. KG.

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