Summary of Results

Rhodiola rosea Extract WS® 1375 (Rosalin®) in Subjects with Life Stress Symptoms

EudraCT No. 2008-002134-29

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First subject included: 09 March 2009

Last subject last visit: 11 August 2009

This document contains in the following sections:

Results Analysis: Numerical Analogue Scales of Subjective Stress Symptoms; Perceived Stress Questionnaire;Multidimensional Fatigue Inventory 20; Numbers Connecting Test; Sheehan Disability Scale (partial); Multidimensional Mood State Questionnaire; Clinical global impressions (CGI) - Severity of illness, Global improvement, Therapeutic effect and side effects.

Results Safety: Incidence of AEs.

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SUMMARY

Sponsor:	Dr. Willmar Schwabe GmbH & Co. KG Willmar-Schwabe-Straße 4 76227 Karlsruhe, Germany
Study drug:	Rhodiola rosea Extract WS® 1375 (Rosalin®)
Active ingredient:	Rhodiola rosea Extract WS® 1375, is a dry extract from the roots and rhizomes of Rhodiola rosea L.
Test medication:	One tablet contains: 200 mg of Rhodiola rosea (WS® 1375, Rosalin®), which is an ethanolic (60 % w/w) extract and characterized by a drug/extract ratio of 1.5–5 : 1.
Reference medication:	None
Study title:	Rhodiola rosea Extract WS® 1375 (Rosalin®) in Subjects with Life Stress Symptoms
Study centres:	The study was conducted in 13 study centres in UK.
Study period:	First subject included: 09 March 2009 Last subject last visit: 11 August 2009
Publications:	Edwards D, Heufelder A, Zimmermann A (2012): Therapeutic Effects and Safety of Rhodiola rosea Extract WSW 1375 in Subjects with Life-stress Symptoms – Results of an Open-label Study. Phytother Res 26 (8): 1220-1225

Objectives: The objective of this clinical trial is to describe the therapeutic effects, safety and tolerability of Rhodiola rosea Extract WS® 1375 (Rosalin®) in subjects with Life Stress Symptoms.

Methodology: The study was conducted as an open, multi-centre, single arm study.

Subjects with Life Stress Symptoms were assigned for Rhodiola rosea Extract WS® 1375 (Rosalin®) treatment. They were screened and enrolled in a single treatment group. Treatment effects were measured on changes of stress symptoms, fatigue, quality of life, mood, concentration, and general health. Safety and tolerability were controlled by comparisons of physical examinations, laboratory data and vital signs measurements between baseline and end of treatment as well as by adverse event screening.

Number of subjects included in the study:

	Planned to be included (total sample)	Screened	Safety analysis set	Full analysis set	Per protocol set
All (WS® 1375)	100	109	101	101	82

Diagnosis and main criteria for inclusion: Subjects with Life Stress Symptoms with the following inclusion criteria

1. Male or female outpatients aged 30 to 60 years (both inclusive).
2. Signed informed consent in accordance with the legal requirements.
3. At least 3 of 7 perceived Life Stress Symptoms listed below assessed as ≥ 5 on Numerical Analogue Scales (NAS):

1) Somatic symptoms: gastrointestinal or cardio-vascular disturbances, muscle tension or backache, frequent headaches
2) Loss of zest for life
3) Exhaustion
4) Irritability (Exploding easily at seemingly inconsequential things)
5) Impairment of concentration
6) Feeling of heteronomy
7) Anxiety

4. Multidimensional Fatigue Inventory 20 (MFI-20) score 7 or more at least for one sub-scale.
5. Sufficient language skills, readiness, and ability on the part of the patient to comply with the physician's instructions, respond to all interview questions, and to fill in the self-assessment scales without evident difficulties and without the assistance of an interpreter.

Test and Control preparation, dose and mode of administration:

Run-in Period:
No trial medication

Open treatment period:
Two film-coated tablets of 200 mg Rhodiola rosea extract WS® 1375 per day

Duration of treatment: 4 weeks open treatment, according to the protocol.

Criteria for evaluation:

Treatment course outcome variables:
Due to the pilot character of the study, no differentiation in primary and secondary outcome variables was intended.

Treatment effect outcome variables:

- 7 NASs of Subjective Stress Symptoms

- Perceived Stress Questionnaire (PSQ)
- Multidimensional Fatigue Inventory 20 (MFI-20)
- Numbers Connecting Test
- Sheehan Disability Scale
- Multidimensional Mood State Questionnaire (MDMQ)
- Clinical Global Impressions (CGI)

Safety outcome variables:

- Physical examination
- Vital Signs
- Adverse Events
- Laboratory Tests

Statistical methods:

The aim of the study was to obtain information about the the safety and tolerability of Rhodiola rosea Extract WS® 1375 (Rosalin®) in subjects with life stress symptoms and the course of life stress symptoms while on treatment with Rhodiola rosea Extract WS® 1375 (Rosalin®). Currently, no data are available on the therapeutic effects of Rhodiola rosea Extract WS® 1375 (Rosalin®) in this target population. To this end, a broad spectrum of rating scales were assessed and evaluated in an exploratory data analysis to generate hypotheses regarding the efficacy and to provide a basis for the planning of subsequent studies. Since this study was an open label exploratory trial no hypotheses were formulated and the data were analysed descriptively.

In order to investigate the course of life stress symptoms in subjects treated with Rhodiola rosea Extract WS® 1375 (Rosalin®) for 4 weeks the absolute and relative intraindividual changes between baseline and end of treatment of the outcome parameters described in Section 7 were evaluated. If adequate, time courses of the outcome parameters were analysed as well. Descriptive statistics were computed to

describe the empirical distributions; 95%-confidence intervals for the expected values and medians were calculated. Accordingly, the resulting p-values and the phrase “statistical significance” have to be interpreted in the exploratory sense.

Analysis was primarily based on the full analysis set including all subjects having received Rhodiola rosea Extract WS® 1375 (Rosalin®) at least once and having at least one measurement of one of the rating scales (NAS, PSQ, MFI-20, Numbers Connecting Test, Sheehan Disability Scale, MDMQ, CGI) during the treatment period. Missing values of some items or total scores during treatment period were replaced by the last observation carried forward method. In addition, a per-protocol (PP) analysis was performed including those subjects of the full analysis set without major protocol violations. The assignment to the analysis populations was documented in the analysis plan which was created before starting the statistical evaluation.

Results:

Demographic data:

(absolute (relative) frequency and mean ± standard deviation, [median])

Full analysis set		
		(N=101)
Sex	male female	33 (32.7%) 68 (67.3%)
Age [y]		44.5 ± 7.4 [44.0]
Height [cm]		167.3 ± 9.2 [167.0]
Weight [kg]		75.9 ± 15.2 [75.0]
BMI [kg/m²]		27.1 ± 5.0 [26.9]

Results of analysis:

All outcome parameters showed a steady improvement that was noticeable within 3 days and in almost all cases statistically significant at this early stage. The improvement continued until the end of treatment. Changes at Week 4 (LOCF) to baseline and the significance level of the change at Day 3 and Week 4 (LOCF) are summarised in the tables below.

NASs of Subjective Stress Symptoms

(mean ± standard deviation [median], two-sided Wilcoxon signed-rank test p-value)

Full analysis set							
Symptoms	Baseline (B)	Change D3-B	Change W1-B	Change W4-B	p-value		
					i)	ii)	iii)
Somatic symptoms	[redacted]	[redacted]	[redacted]	[redacted]	<.0001	<.0001	<.0001
Loss of zest for life	[redacted]	[redacted]	[redacted]	[redacted]	<.0001	<.0001	<.0001
Exhaustion	[redacted]	[redacted]	[redacted]	[redacted]	<.0001	<.0001	<.0001
Irritability	[redacted]	[redacted]	[redacted]	[redacted]	<.0001	<.0001	<.0001
Impairment of concentration	[redacted]	[redacted]	[redacted]	[redacted]	<.0001	<.0001	<.0001
Feeling of heteronomy	[redacted]	[redacted]	[redacted]	[redacted]	<.0001	<.0001	<.0001
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	<.0001	<.0001	<.0001

i) Day 3 (D3) vs. Baseline (B), ii) Week 1 (W1) vs. Baseline, iii) Week 4 (W4) vs. Baseline

Perceived Stress Questionnaire

(mean ± standard deviation [median], two-sided Wilcoxon signed-rank test p-value)

Full analysis set			
Subscales	Baseline (B)	Change W4-B	p-value
Harassment	[redacted]	[redacted]	<.0001
Overload	[redacted]	[redacted]	<.0001
Irritability	[redacted]	[redacted]	<.0001
Lack of joy	[redacted]	[redacted]	<.0001
Fatigue	[redacted]	[redacted]	<.0001
Worries	[redacted]	[redacted]	<.0001
Tension	[redacted]	[redacted]	<.0001
PSQ Index	[redacted]	[redacted]	<.0001

High scores indicate high stress levels. The subscales harassment, overload, fatigue and tension comprise 4 items each; the subscale irritability 2, worries 5 and subscale lack of joy comprises 7 items. The PSQ stress score is defined as (sum of all items - 30) / 90.

Multidimensional Fatigue Inventory 20

(mean ± standard deviation [median], two-sided Wilcoxon signed-rank test p-value)

Full analysis set							
Subscales	Baseline (B)	Change D3-B	Change W1-B	Change W4-B	p-value i)	p-value ii)	p-value iii)
General fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Physical fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mental fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced activity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduced motivation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

i) Day 3 (D3) vs. Baseline (B), ii) Week 1 (W1) vs. Baseline, iii) Week 4 (W4) vs. Baseline

High scores indicate increased fatigue

Compared to baseline, the Numbers Connecting Test (tests A-D) showed an average improvement [redacted] seconds (mean ± standard deviation) in the FAS at Week 4 (LOCF). The change was statistically significant (p [redacted], two-sided Wilcoxon signed-rank test).

Numbers Connecting Test (full analysis set)

(mean ± standard deviation [median], two-sided Wilcoxon signed-rank test p-value)

Full analysis set							
	Baseline (B)	Change D3-B	Change W1-B	Change W4-B	p-value i)	p-value ii)	p-value iii)
time [s]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

i) Day 3 (D3) vs. Baseline (B), ii) Week 1 (W1) vs. Baseline, iii) Week 4 (W4) vs. Baseline

Compared to baseline, the total score of the Sheehan Disability Scale (SDS) improved by [redacted] (mean ± standard deviation) in the FAS. The change was statistically significant ([redacted], two-sided Wilcoxon signed-rank test). Changes in the summary statistics are summarised below.

Sheehan Disability Scale (SDS)

(mean ± standard deviation [median], two-sided Wilcoxon signed-rank test p-value)

Full analysis set					
Subscales	Baseline (B)	Change W1-B	Change W4-B	p-value	
				ii)	iii)
Impairment: Work/School	5.66 ± 2.43 [6.0]	-2.40 ± 2.27 [-2.00]	-2.88 ± 2.66 [-3.00]	<.0001	<.0001
Impairment: Social life	6.02 ± 2.74 [6.00]	[redacted]	[redacted]	[redacted]	[redacted]
Impairment: Family life / Home responsibilities	6.52 ± 2.16 [7.00]	-2.93 ± 2.50 [-3.00]	-3.43 ± 2.65 [-3.00]	<.0001	<.0001
Days lost	0.58 ± 1.44 [0.00]	[redacted]	-0.32 ± 1.36 [0.00]	[redacted]	0.0177
Days unproductive	2.42 ± 2.08 [2.00]	[redacted]	-1.69 ± 2.04 [-1.00]	[redacted]	<.0001
Global Impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ii) Week 1 (W1) vs. Baseline, iii) Week 4 (W4) vs. Baseline

Multidimensional Mood State Questionnaire

(mean ± standard deviation [median], two-sided Wilcoxon signed-rank test p-value)

Full analysis set							
Dimension	Baseline (B)	Change D3-B	Change W1-B	Change W4-B	p-value		
					i)	ii)	iii)
Good mood - Bad mood	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alertness – Tiredness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Calmness - Restlessness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

i) Day 3 (D3) vs. Baseline (B), ii) Week 1 (W1) vs. Baseline, iii) Week 4 (W4) vs. Baseline

Severity of illness, as first item of the CGI, improved by [redacted] (mean ± standard deviation) in the FAS from baseline to Week 4 (LOCF). The reduction was statistically significant from Day 3 to Week 4 (LOCF).

Clinical global impressions (CGI) - Severity of illness (full analysis set)

(mean ± standard deviation [median], two-sided Wilcoxon signed-rank test p-value)

Full analysis set							
	Baseline (B)	Change D3-B	Change W1-B	Change W4-B	p-value		
					i)	ii)	iii)
score	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

i) Day 3 (D3) vs. Baseline (B), ii) Week 1 (W1) vs. Baseline, iii) Week 4 (W4) vs. Baseline

Assessments of the CGI items global improvements as well therapeutic effect and side effects at Week 4 are summarised in the tables below.

Clinical global impressions (CGI) - Global improvement at Week 4

(absolute (relative) frequency)

Full analysis set	
Global Improvement:	Week 4
Very much improved	[redacted]
Much improved	[redacted]
Minimally improved	[redacted]
No change	[redacted]
No remark	[redacted]

Clinical global impressions (CGI) - Therapeutic effect and side effects at Week 4

(absolute (relative) frequency)

Full analysis set	
Item:	Week 4
Therapeutic effect	
Complete or nearly complete remission	[redacted]
Partial remission	[redacted]
Slight improvement	[redacted]
Unchanged or worse	[redacted]
No remark	[redacted]
Side effects	
None	[redacted]
Not significant	[redacted]
Significant	[redacted]
Outweigh therapeutic effect	[redacted]
No remark	[redacted]

Evaluation of subgroups

The positive treatment effects of WS® 1375 (Rosalin®) could be confirmed in all analysed subgroups. Age did not influence the treatment effect.

Results of safety analysis

During the treatment period, a total of 36 patients (35.6%) treated with WS® 1375 (Rosalin®) suffered from 54 adverse events. The incidence of AEs in the treatment phase amounted to [redacted] events per day.

Number and incidence of adverse events during the treatment period

(absolute (relative) frequency of patients with adverse events, number of adverse events)

Safety analysis set, N=101	
System organ class Preferred term	**Number of patients(%)**
Any patient with adverse events	**36 (35.6)**
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)**

Frequency of patients with serious adverse events:

No serious adverse events were observed.

Conclusion

This open, multi-centre, single arm study was conducted to describe the safety and tolerability of a twice-daily formulation with 200 mg of Rhodiola rosea (WS® 1375, Rosalin®) and the course of life stress symptoms while on treatment with Rhodiola rosea Extract WS® 1375 (Rosalin®)..

It was planned to include 100 patients of both genders with Life Stress Symptoms that were to be screened and enrolled in a single treatment group. The course of life stress symptoms was to be measured on changes of Stress Symptoms, Fatigue, Quality of Life, Mood, Concentration, and General Health.

Safety and tolerability were to be controlled by comparisons of physical examinations, laboratory data and vital signs measurements between baseline and end of treatment as well as by adverse event.

In total, 109 patients were screened for inclusion into the study in 13 centres. Eight of the screened patients were not enclosed into the treatment phase due to baseline failure and thus did not take study medication. The remaining 101 patients were enrolled and received the investigational treatment at least once. All patients of the safety analysis set provided baseline measurements and could be included in the full analysis set (FAS). Thus the FAS consisted of 101 patients. The per protocol set consisted of 82 patients.

All outcome variables showed a consistent and steady improvement that was statistically significant for all variables at the end of the study. With the exception of the MFI 20 (subscales physical fatigue and reduced activity) and the Perceived Stress Questionnaire (not tested for this time point) this improvement was statistically significant as early as Day 3. These consistent results were confirmed in the per protocol set and the subgroup analyses.

Before starting active treatment, 7 patients (6.9%) experienced 9 adverse events. During the treatment period, a total of 36 patients (35.6%) treated with WS® 1375 (Rosalin®) reported 54 adverse events. The average incidence of AEs per day was only marginally higher during the treatment phase ([redacted]) compared to the pre-treatment phase ([redacted]).

The vast majority of AEs was assessed with unlikely relationship. No serious adverse events were observed.

No mentionable changes regarding laboratory parameters, physical examination, neurological examination, 12 lead ECG, blood pressure, heart rate or weight were observed throughout the course of the study.

In summary, the course of life stress symptoms was favourable in patients who took 2 x 200 mg of WS® 1375 (Rosalin®) over four weeks. Specifically, these patients showed improvement in Stress Symptoms, Fatigue, Quality of Life, Mood, Concentration, and General Health. Safety and tolerability of WS® 1375 (Rosalin®) also presented a favourable profile. The current study gave no hint for any drug specific side effects of WS® 1375 (Rosalin®).