Clinical trial results:
Multi-centre, open-label clinical trial to evaluate the efficacy and safety of Rhodiola rosea extract (Rosalin) in Subjects with Burnout Symptoms

Summary

EudraCT number	2010-022686-10
Trial protocol	AT
Global end of trial date	24 February 2014

Results information

Result version number	v1 (current)
This version publication date	01 March 2016
First version publication date	02 August 2015

Trial information

Trial identification

Sponsor protocol code	578001.01.012

Additional study identifiers

ISRCTN number	ISRCTN31235821
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Willmar Schwabe GmbH & Co. KG
Sponsor organisation address	Willmar Schwabe Str. 4, Karlsruhe, Germany, 76227
Public contact	Clinical Research Department, Dr. W. Schwabe GmbH & Co. KG, +49 (0)714005573,
Scientific contact	Clinical Research Department, Dr. W. Schwabe GmbH & Co. KG, +49 (0)714005573,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 February 2014
Global end of trial reached?	Yes
Global end of trial date	24 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the trial is to describe the therapeutic effects, safety and tolerability of Rhodiola rosea extract (Rosalin) in subjects with Burnout symptoms

Protection of trial subjects:

Possibility to withdraw consent by subjects. Monitoring of adverse events and laboratory parameters.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 131
Worldwide total number of subjects	131
EEA total number of subjects	131

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	131
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were recruited in four investigational sites.

Pre-assignment period milestones

Number of subjects started	131
Number of subjects completed	118

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 12
Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Baseline

Arm description:

Baseline before starting treatment with Rhodiola rosea extract (Rosalin)

Arm type	Baseline

No investigational medicinal product assigned in this arm

Arm title	Rhodiola rosea extract (Rosalin)

Arm description:

Investigational medical product containing (Rosalin), two film-coated tablets of 200 mg Rhodiola rosea extract

Arm type	Experimental
Investigational medicinal product name	Rhodiola rosea extract (Rosalin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1 film-coated tablet 2 times per day for 12 consecutive weeks

Number of subjects in period 1	Baseline	Rhodiola rosea extract (Rosalin)
Started	118	118
Completed	118	100
Not completed	0	18
private reasons	-	1
Physician decision	-	1
Adverse event, non-fatal	-	4
Lost to follow-up	-	8
Lack of efficacy	-	4

Baseline characteristics

Reporting groups[1]

Reporting group title	Treatment period (overall period)

Reporting group description:

In total, 118 subjects received the investigational treatment.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: In total, 13 of the 131 subjects screened for inclusion into the study were not included into the baseline period.

Reporting group values	Treatment period (overall period)	Total	
Number of subjects	118	118	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	118	118	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	43.5		
standard deviation	± 8.1	-	
Gender categorical Units: Subjects			
Female	69	69	
Male	49	49	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set consists of all subjects having received investigational product at least once and having at least one post baseline measurement of one of the rating scales

Reporting group values	Full analysis set		
Number of subjects	117		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		

Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	117		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean	43.7		
standard deviation	± 8		
Gender categorical			
Units: Subjects			
Female	68		
Male	49		

End points

End points reporting groups

Reporting group title	Baseline

Reporting group description:

Baseline before starting treatment with Rhodiola rosea extract (Rosalin)

Reporting group title	Rhodiola rosea extract (Rosalin)

Reporting group description:

Investigational medical product containing (Rosalin), two film-coated tablets of 200 mg Rhodiola rosea extract

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set consists of all subjects having received investigational product at least once and having at least one post baseline measurement of one of the rating scales

Primary: Change in subscale depersonalisation of the Maslach-Burnout-Inventory (MBI) between baseline and end of treatment

End point title	Change in subscale depersonalisation of the Maslach-Burnout-Inventory (MBI) between baseline and end of treatment

End point description:

The 25-question Maslach Burnout Inventory consists of the four subscales emotional exhaustion (9 items), depersonalisation (5 items), involvement (3 items) and personal accomplishment (8 items). Each item is rated by the subject on the two dimension frequency using a scale from 0 = never to 6 = every day.

Subscale depersonalisation: Items 5, 10, 11, 15, and 22. The score is calculated by the sum of all items responded to divided by the number of items responded to. Higher scores indicate a higher burnout level.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	1.83 (± 1.21)	1.4 (± 1.28)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	-0.2
Variability estimate	Standard deviation
Dispersion value	1.22

Notes:

[1] - Within-subject change between baseline and end of treatment

Primary: Change in subscale emotional exhaustion of the Maslach-Burnout-Inventory (MBI) between baseline and end of treatment

End point title	Change in subscale emotional exhaustion of the Maslach-Burnout-Inventory (MBI) between baseline and end of treatment

End point description:

The 25-question Maslach Burnout Inventory consists of the four subscales emotional exhaustion (9 items), depersonalisation (5 items), involvement (3 items) and personal accomplishment (8 items). Each item is rated by the subject on the two dimension frequency using a scale from 0 = never to 6 = every day.

Subscale emotional exhaustion: Items 1, 2, 3, 6, 8, 13, 14, 16, and 20. The score is calculated by the sum of all items responded to divided by the number of items responded to. Higher scores indicate a higher burnout level.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2.57 (± 0.3)	2.29 (± 1.04)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0003
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	-0.1
Variability estimate	Standard deviation
Dispersion value	1.02

Notes:

[2] - Within-subject change between baseline and end of treatment

Primary: Change in subscale involvement of the Maslach-Burnout-Inventory (MBI) between baseline and end of treatment

End point title	Change in subscale involvement of the Maslach-Burnout-Inventory (MBI) between baseline and end of treatment

End point description:

The 25-question Maslach Burnout Inventory consists of the four subscales emotional exhaustion (9 items), depersonalisation (5 items), involvement (3 items) and personal accomplishment (8 items). Each item is rated by the subject on the two dimension frequency using a scale from 0 = never to 6 = every day.

Subscale involvement: Items 23, 24, and 25. The score is calculated by the sum of all items responded to divided by the number of items responded to. Higher scores indicate a higher burnout level.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2.13 (± 1.31)	2.03 (± 1.31)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.1714
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3
upper limit	0.1
Variability estimate	Standard deviation
Dispersion value	1.32

Notes:

[3] - Within-subject change between baseline and end of treatment

Primary: Change in subscale personal accomplishment of the Maslach-Burnout-Inventory (MBI) between baseline and end of treatment

End point title	Change in subscale personal accomplishment of the Maslach-Burnout-Inventory (MBI) between baseline and end of treatment

End point description:

The 25-question Maslach Burnout Inventory consists of the four subscales emotional exhaustion (9 items), depersonalisation (5 items), involvement (3 items) and personal accomplishment (8 items). Each item is rated by the subject on the two dimension frequency using a scale from 0 = never to 6 = every day.
Subscale personal accomplishment: Items 4, 7, 9, 12, 17, 18, 19, and 21. The score is calculated by the

sum of all items responded to divided by the number of items responded to. Lower scores indicate a higher burnout level.
Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.3 (± 0.41)	4.32 (± 0.94)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.4643
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.2
Variability estimate	Standard deviation
Dispersion value	0.81

Notes:

[4] - Within-subject change between baseline and end of treatment

Primary: Change in global score intensity value of the Burnout Screening Scale (BOSS I) between baseline and end of treatment

End point title	Change in global score intensity value of the Burnout Screening Scale (BOSS I) between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 ('not applicable') to 5 ('highly applicable'). For the global score (all items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally "Breitenwert") and a total average value as a measure for the average stress within the subscale.
Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	116		
Units: points				
arithmetic mean (standard deviation)	2.64 (± 0.71)	1.94 (± 0.69)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 117 subjects, end of treatment values available for 116 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 116 subjects. The number of subjects included in analysis was summarized to 233 (Baseline 117, End of treatment 116) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.6
Variability estimate	Standard deviation
Dispersion value	0.76

Notes:

[5] - Within-subject change between baseline and end of treatment

Primary: Change in global score relative width value of the Burnout Screening Scale (BOSS I) between baseline and end of treatment

End point title	Change in global score relative width value of the Burnout Screening Scale (BOSS I) between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 ('not applicable') to 5 ('highly applicable').
For the global score (all items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally "Breitenwert") and a total average value as a measure for the average stress,

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.3 (± 0.61)	3.45 (± 1.33)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.6
Variability estimate	Standard deviation
Dispersion value	1.2

Notes:

[6] - Within-subject change between baseline and end of treatment

Primary: Change in global score total value of the Burnout Screening Scale (BOSS I) between baseline and end of treatment

End point title	Change in global score total value of the Burnout Screening Scale (BOSS I) between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the global score (all items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress,

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2.31 (± 0.82)	1.44 (± 0.9)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.7
Variability estimate	Standard deviation
Dispersion value	0.88

Notes:

[7] - Within-subject change between baseline and end of treatment

Primary: Change in intensity value of the Burnout Screening Scale (BOSS I) subscale profession between baseline and end of treatment

End point title	Change in intensity value of the Burnout Screening Scale (BOSS I) subscale profession between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale profession (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	114		
Units: points				
arithmetic mean (standard deviation)	2.43 (± 0.81)	1.85 (± 0.71)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 117 subjects, end of treatment values available for 114 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 114 subjects. The number of subjects included in analysis was summarized to 231 (Baseline 117, End of treatment 114) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.4
Variability estimate	Standard deviation
Dispersion value	0.86

Notes:

[8] - Within-subject change between baseline and end of treatment

Primary: Change in relative width value of the Burnout Screening Scale (BOSS I) subscale profession between baseline and end of treatment

End point title	Change in relative width value of the Burnout Screening Scale (BOSS I) subscale profession between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale profession (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	3.98 (± 0.93)	3.23 (± 1.46)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.5
Variability estimate	Standard deviation
Dispersion value	1.32

Notes:

[9] - Within-subject change between baseline and end of treatment

Primary: Change in total value of the Burnout Screening Scale (BOSS I) subscale profession between baseline and end of treatment

End point title	Change in total value of the Burnout Screening Scale (BOSS I) subscale profession between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale profession (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2 (± 0.93)	1.29 (± 0.88)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.5
Variability estimate	Standard deviation
Dispersion value	0.98

Notes:

[10] - Within-subject change between baseline and end of treatment

Primary: Change in intensity value of the Burnout Screening Scale (BOSS I) subscale person itself between baseline and end of treatment

End point title	Change in intensity value of the Burnout Screening Scale (BOSS I) subscale person itself between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale person itself (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary
End point timeframe:	
Baseline and End of Treatment (12-week treatment period).	

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	114		
Units: points				
arithmetic mean (standard deviation)	2.75 (± 0.82)	1.92 (± 0.79)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 117 subjects, end of treatment values available for 114 subjects; LOCF; two-sided,
confidence interval for mean difference is based on t-distribution evaluated for 114 subjects. The number of subjects included in analysis was summarized to 231 (Baseline 117, End of treatment 114) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.7
Variability estimate	Standard deviation
Dispersion value	0.93

Notes:

[11] - Within-subject change between baseline and end of treatment

Primary: Change in relative width value of the Burnout Screening Scale (BOSS I) subscale person itself between baseline and end of treatment

End point title	Change in relative width value of the Burnout Screening Scale (BOSS I) subscale person itself between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale person itself (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.46 (± 0.64)	3.53 (± 1.44)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.7
Variability estimate	Standard deviation
Dispersion value	1.35

Notes:

[12] - Within-subject change between baseline and end of treatment

Primary: Change in total value of the Burnout Screening Scale (BOSS I) subscale person itself between baseline and end of treatment

End point title	Change in total value of the Burnout Screening Scale (BOSS I) subscale person itself between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 ('not applicable') to 5 ('highly applicable').

For the subscale person itself (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally "Breitenwert") and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2.49 (± 0.91)	1.47 (± 0.98)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-1.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.8
Variability estimate	Standard deviation
Dispersion value	1.02

Notes:

[13] - Within-subject change between baseline and end of treatment

Primary: Change in intensity value of the Burnout Screening Scale (BOSS I) subscale family between baseline and end of treatment

End point title	Change in intensity value of the Burnout Screening Scale (BOSS I) subscale family between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale family (5 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	112		
Units: points				
arithmetic mean (standard deviation)	2.86 (± 0.94)	2.22 (± 1.02)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 117 subjects, end of treatment values available for 112 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 112 subjects. The number of subjects included in analysis was summarized to 229 (Baseline 117, End of treatment 112) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)

Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.5
Variability estimate	Standard deviation
Dispersion value	1.08

Notes:

[14] - Within-subject change between baseline and end of treatment

Primary: Change in relative width value of the Burnout Screening Scale (BOSS I) subscale family between baseline and end of treatment

End point title	Change in relative width value of the Burnout Screening Scale (BOSS I) subscale family between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale family (5 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.58 (± 0.7)	3.77 (± 1.46)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.6
Variability estimate	Standard deviation
Dispersion value	1.39

Notes:

[15] - Within-subject change between baseline and end of treatment

Primary: Change in total value of the Burnout Screening Scale (BOSS I) subscale family between baseline and end of treatment

End point title	Change in total value of the Burnout Screening Scale (BOSS I) subscale family between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale family (5 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2.66 (± 1.05)	1.73 (± 1.1)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.7
Variability estimate	Standard deviation
Dispersion value	1.06

Notes:

[16] - Within-subject change between baseline and end of treatment

Primary: Change in intensity value of the Burnout Screening Scale (BOSS I) subscale friends between baseline and end of treatment

End point title	Change in intensity value of the Burnout Screening Scale (BOSS I) subscale friends between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale friends (5 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	107		
Units: points				
arithmetic mean (standard deviation)	2.52 (± 0.9)	1.92 (± 0.77)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 117 subjects, end of treatment values available for 107 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 107 subjects. The number of subjects included in analysis was summarized to 224 (Baseline 117, End of treatment 107) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.5
Variability estimate	Standard deviation
Dispersion value	0.84

Notes:

[17] - Within-subject change between baseline and end of treatment

Primary: Change in relative width value of the Burnout Screening Scale (BOSS I) subscale friends between baseline and end of treatment

End point title	Change in relative width value of the Burnout Screening Scale (BOSS I) subscale friends between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale friends (5 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total

average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary
End point timeframe:	
Baseline and End of Treatment (12-week treatment period).	

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.32 (± 0.97)	3.44 (± 1.71)		

Statistical analyses

Statistical analysis title	Non-parametric analysis
Statistical analysis description:	
Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.	

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.6
Variability estimate	Standard deviation
Dispersion value	1.62

Notes:

[18] - Within-subject change between baseline and end of treatment

Primary: Change in total value of the Burnout Screening Scale (BOSS I) subscale friends between baseline and end of treatment

End point title	Change in total value of the Burnout Screening Scale (BOSS I)

	subscale friends between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS I) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale friends (5 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2.25 (± 1.04)	1.42 (± 1.03)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.7
Variability estimate	Standard deviation
Dispersion value	0.99

Notes:

[19] - Within-subject change between baseline and end of treatment

Primary: Change in global score intensity value of the Burnout Screening Scale (BOSS II) between baseline and end of treatment

End point title	Change in global score intensity value of the Burnout Screening Scale (BOSS II) between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 ('not applicable') to 5 ('highly applicable').

For the global score (all items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally "Breitenwert") and a total average value as a measure for the average stress.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	114		
Units: points				
arithmetic mean (standard deviation)	2.47 (± 0.73)	1.78 (± 0.62)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 117 subjects, end of treatment values available for 114 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 114 subjects. The number of subjects included in analysis was summarized to 231 (Baseline 117, End of treatment 114) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.71

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.6
Variability estimate	Standard deviation
Dispersion value	0.73

Notes:

[20] - Within-subject change between baseline and end of treatment

Primary: Change in global score relative width value of the Burnout Screening Scale (BOSS II) between baseline and end of treatment

End point title	Change in global score relative width value of the Burnout Screening Scale (BOSS II) between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the global score (all items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.01 (± 0.79)	3.04 (± 1.37)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.8
Variability estimate	Standard deviation
Dispersion value	1.22

Notes:

[21] - Within-subject change between baseline and end of treatment

Primary: Change in global score total value of the Burnout Screening Scale (BOSS II) between baseline and end of treatment

End point title	Change in global score total value of the Burnout Screening Scale (BOSS II) between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the global score (all items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2.05 (± 0.86)	1.18 (± 0.81)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	-0.7
Variability estimate	Standard deviation
Dispersion value	0.82

Notes:

[22] - Within-subject change between baseline and end of treatment

Primary: Change in intensity value of the Burnout Screening Scale (BOSS II) subscale physical complaints between baseline and end of treatment

End point title	Change in intensity value of the Burnout Screening Scale (BOSS II) subscale physical complaints between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale physical complaints (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	112		
Units: points				
arithmetic mean (standard deviation)	2.46 (± 0.76)	1.86 (± 0.64)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 117 subjects, end of treatment values available for 112 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 112 subjects. The number of subjects included in analysis was summarized to 229 (Baseline 117, End of treatment 112) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.5
Variability estimate	Standard deviation
Dispersion value	0.75

Notes:

[23] - Within-subject change between baseline and end of treatment

Primary: Change in relative width value of the Burnout Screening Scale (BOSS II) subscale physical complaints between baseline and end of treatment

End point title	Change in relative width value of the Burnout Screening Scale (BOSS II) subscale physical complaints between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale physical complaints (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	3.39 (± 1.09)	2.52 (± 1.23)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.7
Variability estimate	Standard deviation
Dispersion value	1.16

Notes:

[24] - Within-subject change between baseline and end of treatment

Primary: Change in total value of the Burnout Screening Scale (BOSS II) subscale physical complaints between baseline and end of treatment

End point title	Change in total value of the Burnout Screening Scale (BOSS II) subscale physical complaints between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale physical complaints (10 items) three different scores were calculated: an intensity

value as an average measure considering only applicable items, a relative width (originally "Breitenwert") and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	1.69 (± 0.81)	0.99 (± 0.7)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	-0.6
Variability estimate	Standard deviation
Dispersion value	0.75

Notes:

[25] - Within-subject change between baseline and end of treatment

Primary: Change in intensity value of the Burnout Screening Scale (BOSS II) subscale cognitive complaints between baseline and end of treatment

End point title	Change in intensity value of the Burnout Screening Scale (BOSS II) subscale cognitive complaints between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale cognitive complaints (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	112		
Units: points				
arithmetic mean (standard deviation)	2.47 (± 0.89)	1.76 (± 0.74)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 117 subjects, end of treatment values available for 112 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 112 subjects. The number of subjects included in analysis was summarized to 229 (Baseline 117, End of treatment 112) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.6

Variability estimate	Standard deviation
Dispersion value	0.86

Notes:

[26] - Within-subject change between baseline and end of treatment

Primary: Change in relative width value of the Burnout Screening Scale (BOSS II) subscale cognitive complaints between baseline and end of treatment

End point title	Change in relative width value of the Burnout Screening Scale (BOSS II) subscale cognitive complaints between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale cognitive complaints (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.49 (± 0.8)	3.48 (± 1.7)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.7
Variability estimate	Standard deviation
Dispersion value	1.61

Notes:

[27] - Within-subject change between baseline and end of treatment

Primary: Change in total value of the Burnout Screening Scale (BOSS II) subscale cognitive complaints between baseline and end of treatment

End point title	Change in total value of the Burnout Screening Scale (BOSS II) subscale cognitive complaints between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale cognitive complaints (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2.29 (± 1.01)	1.35 (± 1)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1
upper limit	-0.8
Variability estimate	Standard deviation
Dispersion value	0.98

Notes:

[28] - Within-subject change between baseline and end of treatment

Primary: Change in intensity value of the Burnout Screening Scale (BOSS II) subscale emotional complaints between baseline and end of treatment

End point title	Change in intensity value of the Burnout Screening Scale (BOSS II) subscale emotional complaints between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale emotional complaints (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	109		
Units: points				
arithmetic mean (standard deviation)	2.46 (± 0.87)	1.71 (± 0.75)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 117 subjects, end of treatment values available for 109 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 109 subjects. The number of subjects included in analysis was summarized to 226 (Baseline 117, End of treatment 109) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	-0.6
Variability estimate	Standard deviation
Dispersion value	0.86

Notes:

[29] - Within-subject change between baseline and end of treatment

Primary: Change in relative width value of the Burnout Screening Scale (BOSS II) subscale emotional complaints between baseline and end of treatment

End point title	Change in relative width value of the Burnout Screening Scale (BOSS II) subscale emotional complaints between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 (‘not applicable’) to 5 (‘highly applicable’).

For the subscale emotional complaints (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally “Breitenwert”) and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.16 (± 1.13)	3.11 (± 1.69)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	-0.8
Variability estimate	Standard deviation
Dispersion value	1.57

Notes:

[30] - Within-subject change between baseline and end of treatment

Primary: Change in total value of the Burnout Screening Scale (BOSS II) subscale emotional complaints between baseline and end of treatment

End point title	Change in total value of the Burnout Screening Scale (BOSS II) subscale emotional complaints between baseline and end of treatment

End point description:

The Burnout-Screening Scale (BOSS II) is a self-rating scale. All items are evaluated on a scale from 0 ('not applicable') to 5 ('highly applicable').

For the subscale emotional complaints (10 items) three different scores were calculated: an intensity value as an average measure considering only applicable items, a relative width (originally "Breitenwert") and a total average value as a measure for the average stress within the subscale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary
End point timeframe:	
Baseline and End of Treatment (12-week treatment period).	

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2.16 (± 1.1)	1.19 (± 1)		

Statistical analyses

Statistical analysis title	Non-parametric analysis
Statistical analysis description:	
Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.	

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.8
Variability estimate	Standard deviation
Dispersion value	1.02

Notes:

[31] - Within-subject change between baseline and end of treatment

Primary: Change in time of the Numbers Connecting Test (ZVT) between baseline and end of treatment

End point title	Change in time of the Numbers Connecting Test (ZVT) between baseline and end of treatment

End point description:

The Numbers Connecting Test consists of four tests A, B, C, and D. In each test, the time in seconds is recorded that a subject needed to complete the test. The average time for all four tests of each subject was used for evaluation.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: time in seconds				
arithmetic mean (standard deviation)	72.62 (± 19.55)	60.54 (± 15.79)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-12.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.8
upper limit	-10.4
Variability estimate	Standard deviation
Dispersion value	9.24

Notes:

[32] - Within-subject change between baseline and end of treatment

Primary: Change in subjective stress symptom anxiety assessed on a numerical

analogue scale between baseline and end of treatment	
End point title	Change in subjective stress symptom anxiety assessed on a numerical analogue scale between baseline and end of treatment

End point description:

The subjective stress symptom was recorded on a numerical analogue scale which ranges from 0 (‘not impaired at all’) to 10 (‘severely impaired’).

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.45 (± 2.5)	2.69 (± 2.55)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-1.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-1.2
Variability estimate	Standard deviation
Dispersion value	3.02

Notes:

[33] - Within-subject change between baseline and end of treatment

Primary: Change in subjective stress symptom exhaustion assessed on a numerical analogue acale between baseline and end of treatment

End point title	Change in subjective stress symptom exhaustion assessed on a numerical analogue acale between baseline and end of treatment

End point description:

The subjective stress symptom was recorded on a numerical analogue scale which ranges from 0 (‘not impaired at all’) to 10 (‘severely impaired’).

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	6.93 (± 1.59)	3.8 (± 2.75)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-3.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	-2.6
Variability estimate	Standard deviation
Dispersion value	2.83

Notes:

[34] - Within-subject change between baseline and end of treatment

Primary: Change in subjective stress symptom feeling of heteronomy assessed on a numerical analogue scale between baseline and end of treatment

End point title	Change in subjective stress symptom feeling of heteronomy assessed on a numerical analogue scale between baseline and end of treatment

End point description:

The subjective stress symptom was recorded on a numerical analogue scale which ranges from 0 (‘not impaired at all’) to 10 (‘severely impaired’).

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.19 (± 2.72)	2.47 (± 2.52)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.2
upper limit	-1.2
Variability estimate	Standard deviation
Dispersion value	2.89

Notes:

[35] - Within-subject change between baseline and end of treatment

Primary: Change in subjective stress symptom impairment of concentration assessed on a numerical analogue scale between baseline and end of treatment

End point title	Change in subjective stress symptom impairment of concentration assessed on a numerical analogue scale between baseline and end of treatment

End point description:

The subjective stress symptom was recorded on a numerical analogue scale which ranges from 0 (‘not impaired at all’) to 10 (‘severely impaired’).

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	5.79 (± 1.97)	3.31 (± 2.6)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was

summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-2.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-2
Variability estimate	Standard deviation
Dispersion value	2.62

Notes:

[36] - Within-subject change between baseline and end of treatment

Primary: Change in subjective stress symptom irritability assessed on a numerical analogue scale between baseline and end of treatment

End point title	Change in subjective stress symptom irritability assessed on a numerical analogue scale between baseline and end of treatment

End point description:

The subjective stress symptom was recorded on a numerical analogue scale which ranges from 0 (‘not impaired at all’) to 10 (‘severely impaired’).

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	5.53 (± 2.21)	3.23 (± 2.53)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-2.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	-1.8
Variability estimate	Standard deviation
Dispersion value	2.76

Notes:

[37] - Within-subject change between baseline and end of treatment

Primary: Change in subjective stress symptom loss of zest for life assessed on a numerical analogue scale between baseline and end of treatment

End point title	Change in subjective stress symptom loss of zest for life assessed on a numerical analogue scale between baseline and end of treatment

End point description:

The subjective stress symptom was recorded on a numerical analogue scale which ranges from 0 (‘not impaired at all’) to 10 (‘severely impaired’).

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	4.76 (± 2.47)	2.61 (± 2.52)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[38]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	-1.7
Variability estimate	Standard deviation
Dispersion value	2.55

Notes:

[38] - Within-subject change between baseline and end of treatment

Primary: Change in subjective stress somatic symptoms assessed on a numerical analogue scale between baseline and end of treatment

End point title	Change in subjective stress somatic symptoms assessed on a numerical analogue scale between baseline and end of treatment

End point description:

The subjective stress symptom was recorded on a numerical analogue scale which ranges from 0 (‘not impaired at all’) to 10 (‘severely impaired’).

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	5.75 (± 2.06)	3.33 (± 2.61)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-2
Variability estimate	Standard deviation
Dispersion value	2.5

Notes:

[39] - Within-subject change between baseline and end of treatment

Primary: Change in score of subjective stress symptoms assessed on a numerical analogue scale between baseline and end of treatment

End point title	Change in score of subjective stress symptoms assessed on a numerical analogue scale between baseline and end of treatment

End point description:

Seven items of subjective stress symptoms were assessed on numerical analogue scales which range from 0 ('not impaired at all') to 10 ('severely impaired').

The sum of all subjective stress symptom items/7 was evaluated as a total score for subjective stress symptoms.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables

was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary
End point timeframe:	
Baseline and End of Treatment (12-week treatment period).	

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	5.34 (± 1.22)	3.06 (± 2.12)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-2.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	-1.9
Variability estimate	Standard deviation
Dispersion value	1.98

Notes:

[40] - Within-subject change between baseline and end of treatment

Primary: Change in numerical analogue scale for impairment of sexual life between baseline and end of treatment

End point title	Change in numerical analogue scale for impairment of sexual life between baseline and end of treatment

End point description:

The numerical analogue scale (NAS) for Impairment of Sexual Life is a single item (overall satisfaction with sexual life) and ranges from 0 (‘not impaired at all’) to 10 (‘severely impaired’).

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	6.8 (± 1.53)	4.17 (± 3.09)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[41]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-2.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	-2.1
Variability estimate	Standard deviation
Dispersion value	2.81

Notes:

[41] - Within-subject change between baseline and end of treatment

Primary: Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'thinking about sex with interest / desire' between baseline and end of treatment

End point title	Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'thinking about sex with interest / desire' between baseline and end of treatment

End point description:

A 7-point scale was provided in order to rate the change compared to the reference state from 1 ('absent' or 'greatly reduced') to 7 ('greatly increased'), or a 'not applicable' answer is given instead.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	116		
Units: points				
arithmetic mean (standard deviation)	2.72 (± 1.51)	3.32 (± 1.4)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 116 subjects, end of treatment values available for 116 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 116 subjects. The number of subjects included in analysis was summarized to 232 (Baseline 116, End of treatment 116) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.8

Variability estimate	Standard deviation
Dispersion value	1.33

Notes:

[42] - Within-subject change between baseline and end of treatment

Primary: Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'enjoyment of sex' between baseline and end of treatment

End point title	Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'enjoyment of sex' between baseline and end of treatment

End point description:

A 7-point scale was provided in order to rate the change compared to the reference state from 1 ('absent' or 'greatly reduced') to 7 ('greatly increased'), or a 'not applicable' answer is given instead.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	112		
Units: points				
arithmetic mean (standard deviation)	2.63 (± 1.28)	3.25 (± 1.33)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 115 subjects, end of treatment values available for 112 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 112 subjects. The number of subjects included in analysis was summarized to 227 (Baseline 115, End of treatment 112) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	other[43]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	0.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.8
Variability estimate	Standard deviation
Dispersion value	1.3

Notes:

[43] - Within-subject change between baseline and end of treatment

Primary: Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'ability to become sexually aroused' between baseline and end of treatment

End point title	Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'ability to become sexually aroused' between baseline and end of treatment

End point description:

A 7-point scale was provided in order to rate the change compared to the reference state from 1 ('absent' or 'greatly reduced') to 7 ('greatly increased'), or a 'not applicable' answer is given instead.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	114		
Units: points				
arithmetic mean (standard deviation)	2.85 (± 1.36)	3.38 (± 1.24)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 116 subjects, end of treatment values available for 114 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 114 subjects. The number of subjects included in analysis was summarized to 230 (Baseline 116, End of treatment 114) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other[44]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.7
Variability estimate	Standard deviation
Dispersion value	1.3

Notes:

[44] - Within-subject change between baseline and end of treatment

Primary: Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'frequency of sexual activity' between baseline and end of treatment

End point title	Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'frequency of sexual activity' between baseline and end of treatment

End point description:

A 7-point scale was provided in order to rate the change compared to the reference state from 1 ('absent' or 'greatly reduced') to 7 ('greatly increased'), or a 'not applicable' answer is given instead.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	113		
Units: points				
arithmetic mean (standard deviation)	2.17 (± 1.21)	2.81 (± 1.4)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 115 subjects, end of treatment values available for 113 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 113 subjects.

The number of subjects included in analysis was summarized to 228 (Baseline 115, End of treatment 113) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.9
Variability estimate	Standard deviation
Dispersion value	1.28

Notes:

[45] - Within-subject change between baseline and end of treatment

Primary: Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'ability to have orgasm' between baseline and end of treatment

End point title	Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'ability to have orgasm' between baseline and end of treatment

End point description:

A 7-point scale was provided in order to rate the change compared to the reference state from 1 ('absent' or 'greatly reduced') to 7 ('greatly increased'), or a 'not applicable' answer is given instead.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	116	114		
Units: points				
arithmetic mean (standard deviation)	2.98 (± 1.27)	3.27 (± 1.15)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 116 subjects, end of treatment values available for 114 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 114 subjects. The number of subjects included in analysis was summarized to 230 (Baseline 116, End of treatment 114) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	= 0.0052
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.5
Variability estimate	Standard deviation
Dispersion value	1.05

Notes:

[46] - Within-subject change between baseline and end of treatment

Primary: Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item ‘overall satisfaction with sexual life‘ between baseline and end of treatment

End point title	Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item ‘overall satisfaction with sexual life‘ between baseline and end of treatment

End point description:

A 7-point scale was provided in order to rate the change compared to the reference state from 1 (‘absent’ or ‘greatly reduced’) to 7 (‘greatly increased’), or a ‘not applicable’ answer is given instead.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113	114		
Units: points				
arithmetic mean (standard deviation)	2.5 (± 1.09)	3.15 (± 1.2)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 113 subjects, end of treatment values available for 114 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 112 subjects. The number of subjects included in analysis was summarized to 227 (Baseline 113, End of treatment 114) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	227
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.9
Variability estimate	Standard deviation
Dispersion value	1.23

Notes:

[47] - Within-subject change between baseline and end of treatment

Primary: Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item ‘ability to have and/or maintain an erection‘ between baseline and end of treatment

End point title	Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item ‘ability to have and/or maintain an erection‘ between baseline and end of treatment

End point description:

A 7-point scale was provided in order to rate the change compared to the reference state from 1 (‘absent’ or ‘greatly reduced’) to 7 (‘greatly increased’), or a ‘not applicable’ answer is given instead.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[48]	49[49]		
Units: points				
arithmetic mean (standard deviation)	3.22 (± 0.94)	3.63 (± 0.88)		

Notes:

[48] - only male subjects

[49] - only male subjects

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 49 male subjects, end of treatment values available for 49 male subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 49 male subjects. The number of subjects included in analysis was summarized to 98 (Baseline 49, End of treatment 49) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other[50]
P-value	= 0.0015
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.6
Variability estimate	Standard deviation
Dispersion value	0.81

Notes:

[50] - Within-subject change between baseline and end of treatment

Primary: Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'ability to ejaculate' between baseline and end of treatment

End point title	Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item 'ability to ejaculate' between baseline and end of treatment

End point description:

A 7-point scale was provided in order to rate the change compared to the reference state from 1 ('absent' or 'greatly reduced') to 7 ('greatly increased'), or a 'not applicable' answer is given instead.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[51]	49[52]		
Units: points				
arithmetic mean (standard deviation)	3.65 (± 0.86)	3.69 (± 0.71)		

Notes:

[51] - only male subjects

[52] - only male subjects

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline values available for 49 male subjects, end of treatment values available for 49 male subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution evaluated for 49 male subjects. The number of subjects included in analysis was summarized to 98 (Baseline 49, End of treatment 49) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.7449
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.2
Variability estimate	Standard deviation
Dispersion value	0.68

Notes:

[53] - Within-subject change between baseline and end of treatment

Primary: Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item ‘relevance of sexual functioning for current wellbeing‘ between baseline and end of treatment

End point title	Change in rating of the Patient Sexual Function Questionnaire (PSFQ) item ‘relevance of sexual functioning for current wellbeing‘ between baseline and end of treatment

End point description:

A 7-point scale was provided in order to rate the change compared to the reference state from 1 (‘absent’ or ‘greatly reduced’) to 7 (‘greatly increased’), or a ‘not applicable’ answer is given instead.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the

database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	3.85 (± 1.44)	3.77 (± 1.59)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[54]
P-value	= 0.6093
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.2
Variability estimate	Standard deviation
Dispersion value	1.72

Notes:

[54] - Within-subject change between baseline and end of treatment

Primary: Change in Perceived Stress Questionnaire (PSQ) stress score between baseline and end of treatment

End point title	Change in Perceived Stress Questionnaire (PSQ) stress score between baseline and end of treatment

End point description:

The Perceived Stress Questionnaire (PSQ) contains 30 questions. The person rates whether a statement is true on scale which ranges from 1 (‘almost never’) to 4 (‘usually’). For the calculation of scores for the seven subscales and the stress score the items 01, 07, 10, 13, 17, 21, 25, and 29 will be reversed

according to their positive assessment by calculating 5 minus item value.

The PSQ stress score is calculated as: (sum of all items - 30) / 90

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	0.6 (± 0.15)	0.44 (± 0.2)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	-0.1
Variability estimate	Standard deviation
Dispersion value	0.18

Notes:

[55] - Within-subject change between baseline and end of treatment

Primary: Change in Perceived Stress Questionnaire (PSQ) subscale fatigue between

baseline and end of treatment	
End point title	Change in Perceived Stress Questionnaire (PSQ) subscale fatigue between baseline and end of treatment

End point description:

The Perceived Stress Questionnaire (PSQ) contains 30 questions. The person rates whether a statement is true on scale which ranges from 1 (‘almost never’) to 4 (‘usually’). For the calculation of scores for the seven subscales and the stress score the items 01, 07, 10, 13, 17, 21, 25, and 29 will be reversed according to their positive assessment by calculating 5 minus item value.

The subscale fatigue is calculated as the sum of the items 01; 08; 13; 15.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	12.47 (± 2.14)	10.06 (± 3.08)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Rhodiola rosea extract (Rosalin) v Baseline
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[56]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	-1.9

Variability estimate	Standard deviation
Dispersion value	3.03

Notes:

[56] - Within-subject change between baseline and end of treatment

Primary: Change in Perceived Stress Questionnaire (PSQ) subscale harassment between baseline and end of treatment

End point title	Change in Perceived Stress Questionnaire (PSQ) subscale harassment between baseline and end of treatment

End point description:

The Perceived Stress Questionnaire (PSQ) contains 30 questions. The person rates whether a statement is true on scale which ranges from 1 ('almost never') to 4 ('usually'). For the calculation of scores for the seven subscales and the stress score the items 01, 07, 10, 13, 17, 21, 25, and 29 will be reversed according to their positive assessment by calculating 5 minus item value.

The subscale harassment is calculated as the sum of the items 02; 06; 19; 24.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	10.05 (± 2.34)	8.56 (± 2.62)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	-1
Variability estimate	Standard deviation
Dispersion value	2.52

Notes:

[57] - Within-subject change between baseline and end of treatment

Primary: Change in Perceived Stress Questionnaire (PSQ) subscale irritability between baseline and end of treatment

End point title	Change in Perceived Stress Questionnaire (PSQ) subscale irritability between baseline and end of treatment

End point description:

The Perceived Stress Questionnaire (PSQ) contains 30 questions. The person rates whether a statement is true on scale which ranges from 1 (‘almost never’) to 4 (‘usually’). For the calculation of scores for the seven subscales and the stress score the items 01, 07, 10, 13, 17, 21, 25, and 29 will be reversed according to their positive assessment by calculating 5 minus item value.

The subscale irritability is calculated as the sum of the items 03; 10.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	5.73 (± 1.34)	4.63 (± 1.56)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[58]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.8
Variability estimate	Standard deviation
Dispersion value	1.53

Notes:

[58] - Within-subject change between baseline and end of treatment

Primary: Change in Perceived Stress Questionnaire (PSQ) subscale lack of joy between baseline and end of treatment

End point title	Change in Perceived Stress Questionnaire (PSQ) subscale lack of joy between baseline and end of treatment

End point description:

The Perceived Stress Questionnaire (PSQ) contains 30 questions. The person rates whether a statement is true on scale which ranges from 1 (‘almost never’) to 4 (‘usually’). For the calculation of scores for the seven subscales and the stress score the items 01, 07, 10, 13, 17, 21, 25, and 29 will be reversed according to their positive assessment by calculating 5 minus item value.

The subscale lack of joy is calculated as the sum of the items 05; 07; 16; 17; 21; 23; 25.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	19.26 (± 3.69)	16.49 (± 4.59)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-2.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	-2
Variability estimate	Standard deviation
Dispersion value	4.14

Notes:

[59] - Within-subject change between baseline and end of treatment

Primary: Change in Perceived Stress Questionnaire (PSQ) subscale overload between baseline and end of treatment

End point title	Change in Perceived Stress Questionnaire (PSQ) subscale overload between baseline and end of treatment

End point description:

The Perceived Stress Questionnaire (PSQ) contains 30 questions. The person rates whether a statement is true on scale which ranges from 1 (‘almost never’) to 4 (‘usually’). For the calculation of scores for the seven subscales and the stress score the items 01, 07, 10, 13, 17, 21, 25, and 29 will be reversed according to their positive assessment by calculating 5 minus item value.

The subscale overload is calculated as the sum of the items 04; 11; 28; 29

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	11.57 (± 2.62)	10.21 (± 2.89)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[60]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-1.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-0.9
Variability estimate	Standard deviation
Dispersion value	2.32

Notes:

[60] - Within-subject change between baseline and end of treatment

Primary: Change in Perceived Stress Questionnaire (PSQ) subscale tension between baseline and end of treatment

End point title	Change in Perceived Stress Questionnaire (PSQ) subscale tension between baseline and end of treatment

End point description:

The Perceived Stress Questionnaire (PSQ) contains 30 questions. The person rates whether a statement is true on scale which ranges from 1 (‘almost never’) to 4 (‘usually’). For the calculation of scores for the seven subscales and the stress score the items 01, 07, 10, 13, 17, 21, 25, and 29 will be reversed according to their positive assessment by calculating 5 minus item value.

The subscale tension is calculated as the sum of the items 12; 14; 26; 27.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the

database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	11.74 (± 2.09)	9.32 (± 2.96)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[61]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.9
upper limit	-1.9
Variability estimate	Standard deviation
Dispersion value	2.6

Notes:

[61] - Within-subject change between baseline and end of treatment

Primary: Change in Perceived Stress Questionnaire (PSQ) subscale worries between baseline and end of treatment

End point title	Change in Perceived Stress Questionnaire (PSQ) subscale worries between baseline and end of treatment

End point description:

The Perceived Stress Questionnaire (PSQ) contains 30 questions. The person rates whether a statement

is true on scale which ranges from 1 (‘almost never’) to 4 (‘usually’). For the calculation of scores for the seven subscales and the stress score the items 01, 07, 10, 13, 17, 21, 25, and 29 will be reversed according to their positive assessment by calculating 5 minus item value.

The subscale worries is calculated as the sum of the items 09; 18; 20; 22; 30.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	12.86 (± 3.08)	10.74 (± 3.25)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[62]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-2.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.7
upper limit	-1.5
Variability estimate	Standard deviation
Dispersion value	3.21

Notes:

[62] - Within-subject change between baseline and end of treatment

Primary: Change in global impairment score of the Sheehan Disability Scale between baseline and end of treatment

End point title	Change in global impairment score of the Sheehan Disability Scale between baseline and end of treatment

End point description:

The Sheehan Disability Scale is a brief self-report (patient-rated) inventory. All items are scored on a 0-10 scale, where 0 represents no impairment, 1-3 mild impairment, 4-6 moderate impairment, 7-9 marked impairment and 10 extreme impairments.

A total score named "global impairment" is calculated as the sum of the first three items of the questionnaire.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	17.83 (± 5.76)	12.39 (± 7.7)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-5.44

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	-4.2
Variability estimate	Standard deviation
Dispersion value	6.91

Notes:

[63] - Within-subject change between baseline and end of treatment

Primary: Change in Sheehan Disability Scale item 'days lost' between baseline and end of treatment

End point title	Change in Sheehan Disability Scale item 'days lost' between baseline and end of treatment

End point description:

The Sheehan Disability Scale is a brief self-report (patient-rated) inventory. All items are scored on a 0-10 scale, where 0 represents no impairment, 1-3 mild impairment, 4-6 moderate impairment, 7-9 marked impairment and 10 extreme impairments.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	1 (± 2.32)	0.57 (± 1.34)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[64]
P-value	= 0.0628
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8
upper limit	0
Variability estimate	Standard deviation
Dispersion value	2.12

Notes:

[64] - Within-subject change between baseline and end of treatment

Primary: Change in Sheehan Disability Scale item 'days underproductive' between baseline and end of treatment

End point title	Change in Sheehan Disability Scale item 'days underproductive' between baseline and end of treatment

End point description:

The Sheehan Disability Scale is a brief self-report (patient-rated) inventory. All items are scored on a 0-10 scale, where 0 represents no impairment, 1-3 mild impairment, 4-6 moderate impairment, 7-9 marked impairment and 10 extreme impairments.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	2.52 (± 2.38)	1.47 (± 1.75)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data

base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[65]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-0.6
Variability estimate	Standard deviation
Dispersion value	2.47

Notes:

[65] - Within-subject change between baseline and end of treatment

Primary: Change in Multidimensional Mood State Questionnaire (MDMQ) subscale 'alertness – tiredness' between baseline and end of treatment

End point title	Change in Multidimensional Mood State Questionnaire (MDMQ) subscale 'alertness – tiredness' between baseline and end of treatment

End point description:

The Multidimensional Mood State Questionnaire is a self-rating scale to describe three dimensions of mood and wellbeing. Each subscale consists of four adjectives representing the positive and four adjectives representing the negative aspect. Each adjective is rated on a five-point scale ranging from 1 = „not at all" to 5 = „very much".

The scores for the three dimensions are calculated by summing up the item scores for each subscale after inversion of the negative items. Subscale 'alertness – tiredness': positive items 2, 10, 17, 20; negative items: 5, 7, 13, 23.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	20.76 (± 7.16)	26.38 (± 8.02)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[66]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	5.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	4
upper limit	7.2
Variability estimate	Standard deviation
Dispersion value	8.82

Notes:

[66] - Within-subject change between baseline and end of treatment

Primary: Change in Multidimensional Mood State Questionnaire (MDMQ) subscale ' calmness – restlessness' between baseline and end of treatment

End point title	Change in Multidimensional Mood State Questionnaire (MDMQ) subscale ' calmness – restlessness' between baseline and end of treatment

End point description:

The Multidimensional Mood State Questionnaire is a self-rating scale to describe three dimensions of mood and wellbeing. Each subscale consists of four adjectives representing the positive and four adjectives representing the negative aspect. Each adjective is rated on a five-point scale ranging from 1 = „not at all" to 5 = „very much".

The scores for the three dimensions are calculated by summing up the item scores for each subscale after inversion of the negative items. Subscale 'calmness – restlessness': positive items 6, 12, 15, 24; negative items: 3, 9, 19, 22

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	22.26 (± 6.64)	28.24 (± 7.36)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[67]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	5.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.7
upper limit	7.2
Variability estimate	Standard deviation
Dispersion value	6.82

Notes:

[67] - Within-subject change between baseline and end of treatment

Primary: Change in Multidimensional Mood State Questionnaire (MDMQ) subscale 'good mood – bad mood' between baseline and end of treatment

End point title	Change in Multidimensional Mood State Questionnaire (MDMQ) subscale 'good mood – bad mood' between baseline and end of treatment

End point description:

The Multidimensional Mood State Questionnaire is a self-rating scale to describe three dimensions of mood and wellbeing. Each subscale consists of four adjectives representing the positive and four adjectives representing the negative aspect. Each adjective is rated on a five-point scale ranging from 1 = „not at all“ to 5 = „very much“.

The scores for the three dimensions are calculated by summing up the item scores for each subscale after inversion of the negative items. Subscale 'good mood – bad mood': positive items 1, 8, 14, 21; negative items: 4, 11, 16, 18.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary.
Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	24.08 (± 6.23)	29.64 (± 6.82)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[68]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	5.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.3
upper limit	6.9
Variability estimate	Standard deviation
Dispersion value	7.07

Notes:

[68] - Within-subject change between baseline and end of treatment

Primary: Change in Clinical Global Impressions (CGI) Item 'severity of disorder'

between baseline and end of treatment	
End point title	Change in Clinical Global Impressions (CGI) Item 'severity of disorder' between baseline and end of treatment

End point description:

Severity of disorder: range from 0=‘not at all ill’ to 7=’extremely severe ill’

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. Because at least one primary end point is required to enter study results into the database, all outcome variables are presented using the end point type primary. Baseline is defined as the last measurement before first intake of study drug.

End point type	Primary

End point timeframe:

Baseline and End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: points				
arithmetic mean (standard deviation)	3.44 (± 0.72)	2.44 (± 1.14)		

Statistical analyses

Statistical analysis title	Non-parametric analysis

Statistical analysis description:

Baseline and end of treatment values available for 117 subjects; LOCF; two-sided, confidence interval for mean difference is based on t-distribution. The number of subjects included in analysis was summarized to 234 (Baseline 117, End of treatment 117) because of requirements of the Eudra-CT data base.

Comparison groups	Baseline v Rhodiola rosea extract (Rosalin)
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	< 0.0001
Method	Wilcoxon signed-rank test
Parameter estimate	Mean difference (change from baseline)
Point estimate	-0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	-0.8
Variability estimate	Standard deviation
Dispersion value	1.05

Notes:

[69] - Within-subject change between baseline and end of treatment

Secondary: Clinical Global Impressions (CGI) Item 'change from baseline: global improvement' at end of treatment

End point title	Clinical Global Impressions (CGI) Item 'change from baseline: global improvement' at end of treatment

End point description:

Clinical Global Impression of Change could be rated on a 7-point scale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. End point type secondary selected because only descripive statistical analysis planned for this end point.

End point type	Secondary

End point timeframe:

Assessment at End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117[70]	117		
Units: Subjects				
Very much improved	0	41		
Much improved	0	26		
Minimally improved	0	34		
No change	0	9		
Minimally worse	0	5		
Not assessed	0	2		

Notes:

[70] - Not applicable at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions (CGI) Item 'therapeutic effect' at end of treatment

End point title	Clinical Global Impressions (CGI) Item 'therapeutic effect' at end of treatment

End point description:

CGI-item 'therapeutic efficacy' could be rated on a 4-point scale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. End point type secondary selected because only descriptive statistical analysis plannned for this end point.

End point type	Secondary

End point timeframe:

Assessment at End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117[71]	117		
Units: Subjects				
Marked improvement	0	49		
Moderate improvement	0	26		
Minimal improvement	0	30		
Unchanged or worse	0	8		
Not assessed	0	4		

Notes:

[71] - Not applicable at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impressions (CGI) Item 'tolerability: side effects' at end of treatment

End point title	Clinical Global Impressions (CGI) Item 'tolerability: side effects' at end of treatment

End point description:

The CGI item is asking for the relevance of adverse events to functioning in everyday-life and could be rated on a 4-point scale.

Note: Due to the character of the study, no differentiation in primary and secondary outcome variables was intended. End point type secondary selected because only descriptive statistical analysis plannned for this end point.

End point type	Secondary

End point timeframe:

Assessment at End of Treatment (12-week treatment period).

End point values	Baseline	Rhodiola rosea extract (Rosalin)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117[72]	117		
Units: Subjects				
None	0	98		
Do not signif. interfere with patients functioning	0	13		
Significantly interferes with patients functioning	0	4		
Not assessed	0	2		

Notes:
[72] - Not applicable at baseline

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	15
Reporting groups	
Reporting group title	Rhodiola rosea extract (Rosalin)
Reporting group description: Verum treatment	
Reporting group title	No active treatment
Reporting group description: No active treatment	

Serious adverse events	Rhodiola rosea extract (Rosalin)	No active treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 118 (0.85%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Rhodiola rosea extract (Rosalin)	No active treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 118 (38.98%)	2 / 118 (1.69%)	
Nervous system disorders			
Headache			
subjects affected / exposed	30 / 118 (25.42%)	1 / 118 (0.85%)	
occurrences (all)	36	1	
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	12 / 118 (10.17%)	0 / 118 (0.00%)	
occurrences (all)	15	0	
Influenza			
subjects affected / exposed	12 / 118 (10.17%)	1 / 118 (0.85%)	
occurrences (all)	13	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 June 2011	Amendment No. 1: A pregnancy test for women with childbearing potential at weeks 4 and 8 was added to the trial schedule.
27 September 2011	Amendment No. 2: Exclusion criterion 6 was modified in order to allow the enrolment of subjects who received non-medical psychiatric treatment if it was performed in unchanged frequency for at least 6 months and remained unchanged during the course of the trial. Exclusion criterion 7 was modified in order to only allow the enrolment of subjects with intake of any prescribed psychotropic medication in sufficient dosage for a duration of minimum 4 weeks within 6 months before enrolment and no intake of any prescribed psychotropic medication within 2 weeks before enrolment resp. within 5 half-lives of the psychotropic substance

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported