Ergebnisbericht zur Veröffentlichung der Ergebnisse klinischer Prüfungen an die zuständige Bundesoberbehörde gemäß §42b bzw §145 AMG (interne Studiennummer 178S11PF bzw. P1-2011, EucdraCT No.2011-006129-17)

<table>
<tr><td>Name of Sponsor/Company:
PASCOE pharmazeutische Präparate GmbH
Schiffenberger Weg 55
35394 Gießen</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:
Pascoflair® 425 mg</td></tr>
<tr><td>Name of Active Ingredient:
Pascoflair® 425mg: Passionsblumenkraut-Trockenextrakt (5-7:1)</td></tr>
<tr><td colspan="3">Title of Study: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PILOT STUDY ON THE EFFICACY OF PASSIFLORA INCARNATA L. IN AN ACUTE STRESSFUL SITUATION</td></tr>
<tr><td colspan="3">Investigators: Prof. Michael R. Clemens (Principle Investigator), MD,
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Carina Contreras
Irmgard Schröder
Lienhard Stolzis</td></tr>
<tr><td colspan="3">Study centre(s): DAaCRO GmbH & Co. KG
Science Park Trier, Max-Planck-Str. 22; 54296 Trier</td></tr>
<tr><td colspan="3">Protocol version/Amendments: Final 1.0 (14.02.2012)</td></tr>
<tr><td colspan="3">Publication (reference):</td></tr>
<tr><td rowspan="2">Studied period (years):
(date of first enrolment)
June 04, 2012
(date of last completed)
August 13, 2012</td><td colspan="2">Phase of development:
Phase III</td></tr>
<tr><td colspan="2">Study terminated: ☐ Yes ☒ No
Reason for termination:</td></tr>
<tr><td colspan="3">Objectives:
The objective of the study was to investigate the effect of Pascoflair® intake on the psychological and biological stress response to an acute psychosocial stress test (Trier Social Stress Test; TSST). The primary study outcome was to test for an effect on psychological stress during the TSST. For evaluation of psychological stress, the three variables stress perception, anxiety and insecurity were used. The secondary study outcome was to investigate the effect of Pascoflair® on the biological stress response to the stress test and on general well-being, anxiety and sleep.</td></tr>
<tr><td colspan="3">Methodology: This was a randomized, double-blind, placebo-controlled, single-center study with two arms (placebo and verum). During Visit 1 study information and an informed consent form were handed out. After study inclusion on Visit 2, participants were assigned to one of two groups at random and received the test products (either Pascoflair® or a matching placebo). The 3rd visit included the completion of questionnaires regarding well-being and the TSST for inducing acute psychosocial stress. The primary study outcome was measured with visual analogue scales (VAS) before, during and after the TSST. Secondary objectives were measures of the biological stress response such as saliva and serum cortisol, epinephrine and norepinephrine, ACTH as well as heart rate, sympathovagal balance as a measure of heart rate variability, pulse transit time and electrodermal activity. Secondary psychological endpoints were measured with the State-Trait Anxiety Inventory (STAI), Multidimensional</td></tr>
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Mood State Questionnaire (MDBF), the Leeds Sleep Evaluation Questionnaire (LSEQ) and the Profile of Mood State questionnaire (POMS).

Number of patients (planned and analysed): planned 60 subjects Per Protocol / analysed 60 ITT, 58 per protocol

Diagnosis and main criteria for inclusion:

diagnose: healthy subjects

Healthy non-smoking male and female volunteers between 25 to 45 years of age with a Body-mass-index (BMI) ≥ 19 to ≤ 30 kg/m2 that provided a signed written informed consent form. Only females using oral contraceptives for at least 3 months are included in the study.

Test product, dose and mode of administration, batch number:

Pascoflair® 425 mg: 1x 3 coated tablets, oral, Ch.B.:5609

Duration of treatment: 3 x 1 tablet for 3 days

Reference therapy, dose and mode of administration, batch number:

Placebo Tabletten: 1x 3 coated tablets, oral, Ch.B.:5609

Criteria for evaluation:

Efficacy: To investigate the effect of Pascoflair® on psychological stress during an acute psychosocial stress test. For evaluation of psychological stress, the three variables stress perception, anxiety and insecurity are used (tested with VAS).

To investigate the effect of Pascoflair® on general wellbeing, anxiety and sleep as well as on the physiological stress response to the stress test with validated questionnaires (STAI X2, STAI X1, TICS, POMS, LSEQ, MDBF) . Furtheron heart rate, pulse transit time, skin conductance, sympathovagal balance during acute stress; cortisol, ACTH and catecholamines during acute stress were tested.

Safety:

Tolerability, adverse drug reactions were evaluated and safety blood samples were analysed.

Statistical methods: Statistical analyses were done with SPSS Statistics 17.0 and R 2.14.2. All analyses were performed for the ITT and PP population. Data including outliers were only tested outlier-corrected for all parametric tests. Effect sizes (r and partial $\eta 2$) are presented for significant and marginally significant results.

Repeated measures analysis of variance (RMANOVA) and all non-parametric tests were done with SPSS. Calculation of descriptive statistics and mixed models were performed in the environment of R. Mixed models were done with the package lme4.

All raw data are summarized with descriptive statistics (N, mean, median, and standard deviation, standard error, first (1rst) and third (3rd) quartile, minimum and maximum) for the ITT population.

Summary – Conclusions

Efficacy Results:

VAS:

The primary endpoints were stress perception, anxiety and insecurity. These parameters were measured with visual analogue scales (VAS), 100 mm bipolar lines ranging from “not at all” (0 mm) to “highly” (100 mm).There was no significant difference in the psychological stress response between verum and placebo groups.

Females of both groups generally perceived higher stress, anxiety and insecurity as compared to males. However, verum males showed marginally significant less anxiety than males of the control group. Moreover, the verum group was characterized by significantly higher norepinephrine levels before and after the TSST ($p < 0.001$). Norepinephrine levels increased from 581.2 ng/L (± 29.4) to 803.1 ng/L (± 37.5) in the verum group and from 430.3 ng/L (± 22.9) to 670.1 ng/L (± 38.7) in the placebo group. Moreover, the verum group was characterized by marginally higher sympathovagal balance ($p = 0.077$). Sympathovagal balance increased from 22.8 LF/HF*10 (± 1.8) to 45.5 LF/HF*10 (± 3.7) in the verum group and from 18.2 LF/HF*10 (± 1.4) to 44.0 (± 4.5) in the placebo group. In addition, although some sleep parameters enhanced in both groups, results suggest that treatment with Pascoflair® may have been advantageous on sleep quality and behavior following awakening.

a) General observations concerning sleep (LSEQ), profile of mood/ general well-being (POMS) and state anxiety (STAI-X1)
Sleep: Changes in four aspects of sleep were measured: quality of sleep, getting to sleep, awakening from sleep and behavior following awakening using single and summary scales.
Results suggest that sleep quality improved in both groups during the study. Subjects of both groups reported to have less wakeful periods at V3 than at V2. Moreover, both treatment groups felt more alert at V3 as compared to V2. However, several sleep parameters enhanced only in the verum group: Subjects of the verum group felt significantly less drowsy as compared to placebo at V3 and compared to V2. Additionally, individuals of the verum group reported more restful sleep and felt more alert after awakening at V3 than at V2. Furthermore by trend, subjects of the verum group reported to fall asleep easier and more quickly at V3 as compared to V2; though this was only found for the PP population, whereas analyses of the ITT population pointed out that this was true for the whole study population. Due to behavior following awakening the summary scale was significantly higher in the verum than in the placebo group. The change in sleep parameters from V2 to V3 was significantly higher in the verum group as compared to placebo in feeling drowsy, feeling alert upon awakening and in the summary scale for behavior following awakening. Moreover, the changes in falling asleep easier and having a more restful sleep were higher in the verum in comparison to the placebo group.
POMS: Results suggest that the verum group was characterized by marginally higher scores in depression/ anxiety at V2 as well as at V3. There was no significant difference in fatigue, hostility and vigor between verum and placebo. Vigor and fatigue significantly decreased over the study period in both groups, whereas no changes were observed in depression/ anxiety and hostility. There was also no significant difference between verum and placebo regarding the change in POMS scales between V2 and V3.
State anxiety (STAI-X1): State anxiety was marginally higher at V2 in the verum group as compared to placebo (though only in the PP population). There was no difference at V3. Moreover, the increase in state anxiety from V2 to V3 pre-stress was higher in the placebo group as compared to the verum group.
b) The TSST
The TSST induced a significant increase in state anxiety, bad mood, alertness and agitation. The stress test also significantly increased saliva and serum cortisol levels, ACTH, catecholamines (norepinephrine) and measures of the autonomic nervous system (heart rate, sympathovagal balance and electrodermal activity). A decrease in pulse transit time occurred in response to the TSST. These observations suggested that the TSST was a useful method for inducing psycho-social stress.
No significant differences were measurable between verum and placebo in all variables assessed for the psychological stress response during the TSST. Both groups showed a normal stress response towards an acute stressor: Participants experienced similar levels of state anxiety and changes in mood characteristics. When accounting the psychological stress response for sex, it was evident that females perceived more stress, anxiety and insecurity than males. Moreover, verum males showed marginally less anxiety as compared to placebo males.
Cortisol, ACTH, epinephrine, heart rate, pulse transit time and electrodermal activity did not differ between verum and placebo. However, the verum group was characterized by significantly higher pre- and post-stress norepinephrine levels and also by generally higher sympathovagal balance. In an ancillary analysis, it was found that basal norepinephrine levels were positively correlated with alertness (MDBF) and negatively with fatigue (POMS) in the verum group only. Thus, participants with higher norepinephrine levels had lower fatigue and higher alertness before and after the TSST. This was not found for the placebo group. Moreover for the whole study population, higher norepinephrine levels were related to higher ACTH and cortisol (AUCG) production and also a higher cortisol increase. When both groups were analyzed separately this effect diminished completely in the placebo group, whereas positive relationships were found for the verum group only.

In conclusion, the investigational product may not generally lower the acute psychological stress response in healthy subjects but may enhance sleep, especially in subjects with some sleep impairments. Moreover, the investigational product increase norepinephrine levels which in turn may lower signs of fatigue as suggested by ancillary analyses.

Safety Results:

Eleven of 60 subjects reported adverse events (verum: n = 5; placebo: n = 6). The intensity was rated as mild in all cases. Causality was rated as possibly related in 1 case: A female of the verum group

reported an irritable stomach. There were no actions taken with trial medications. In two cases AEs were still ongoing at the end of the study.

Conclusion:

Treatment of Pascoflair® may enhance sleep quality and alertness upon awakening. Ancillary analyses suggest that lower values in fatigue and higher alertness before and after the TSST were associated with higher norepinephrine levels exclusively in the verum group. Norepinephrine reflects wakefulness, attention and concentrativeness, while low norepinephrine levels have shown to be related to symptoms of fatigue, low energy and lack of motivation (Stahl, 2002). Thus, the enhancement in sleep quality and behavior following sleep might be facilitated by higher basal norepinephrine levels.

Date of Report: 25.09.2013