Ergebnisbericht zur Veröffentlichung der Ergebnisse klinischer Prüfungen an die zuständige Bundesoberbehörde gemäß §42b bzw §145 AMG

(interne Studiennummer 200S15PF bzw. NCAG 15/14, EucdraCT No.2015-003369-50)

<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®</td></tr>
<tr><td>Name of Active Ingredient:
Pascoflair®:
Passionsblumenkraut-Trockenextrakt (5-7:1)</td></tr>
<tr><td colspan="3">Title of Study: Proof of effectiveness of PASCOFLAIR® using quantitative measurement of electric brain activity in 40 subjects suffering from test anxiety. A double-blind, randomized, placebo-controlled, 2-armed, Phase IV study in parallel design.</td></tr>
<tr><td colspan="3">Investigators:
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<tr><td colspan="3">Study centre(s):
NeuroCode AG
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<tr><td colspan="3">Protocol version/Amendments: Final 1.0 (18.03.2016)</td></tr>
<tr><td colspan="3">Publication (reference):</td></tr>
<tr><td rowspan="2">Studied period (years):
(date of first enrolment)
13.05.2015
(date of last completed)
20.08.2015</td><td colspan="2">Phase of development:
Phase IV</td></tr>
<tr><td colspan="2">Study terminated: ☐ Yes ☒ No
Reason for termination: -</td></tr>
<tr><td colspan="3">Objectives:
Anxiolytic effects of PASCOFLAIR® shall be tested in subjects suffering from test anxiety after single intake by aid of a newly developed, validated method consisting of a combination of Eye- Tracking (following glances) with Neurocode-Tracking (quantitative EEG with a time resolution of 364 ms) termed "EnkephaloVision".</td></tr>
<tr><td colspan="3">Methodology:</td></tr>
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Quantitative-topographical EEG by measurement of current source density during different cognitive and emotional challenges (Dimpfel et. al., 1996).
Combination of Neurocode-Tracking (quantitative-topographic EEG with epoch length of 364 ms) with Eye-Tracking (following eye gazes) (Dimpfel and Hofmann 2011, Dimpfel 2014, Dimpfel and Morys 2014).

Number of patients (planned and analysed): planned 40 subjects/ analysed 40 subjects

Diagnosis and main criteria for inclusion:
Healthy male and female subjects.
Age between 18 and 40 years (both included).
Test Anxiety questionnaire "PAF" (for pre-selection of subjects) - values above T> 60 are regarded as conclusive.
Subject must be capable of giving informed consent.
Acceptance of written consent to participate in the study after instruction in written and oral form (informed consent).

Test product, dose and mode of administration, batch number:
Pascoflair®, 2 coated tablets, oral, Ch.B.:5609

Duration of treatment: 1 day

Reference therapy, dose and mode of administration, batch number:
Placebo tablets: 2 coated tablets, oral, Ch.B.:5609

Criteria for evaluation:
Efficacy: Primary outcome measures: Comparison of verum and placebo is performed on electric power in 17 different brain regions using six frequency ranges defined as target parameters in the presence of different stress inducing cognitive tests and emotional video scenes (i.e. quiz, memory test, Stroop test). With respect to cognition and emotion changes in frontal and temporal spectral beta power are evaluated.

Safety: Secondary outcome measures are tolerability and a correlation between questionnaire score and spectral EEG power with regard to beta frequency ranges.

Statistical methods: EEG data from the first recording session before intake of the capsules are given as absolute numbers (μV2). For explorative statistical evaluation the nonparametric Wilcoxon test was used. For mathematical differentiation of the different mental loads the linear discriminant analysis according to Fischer was used. Results from the first three discriminant functions were projected into space (X, Y and Z coordinates), whereas results from the fourth to sixth discriminant functions were coded into red, green and blue colour, respectively, followed by an additive colour mixture (so-called RGB-mode). In order to document statistically the different electric reactions of the brain to various cognitive and emotional loads, data from each part of the presentation were divided by the data obtained during watching a fixation cross on the monitor (1 minute) at the beginning. Comparison of PASCOFLAIR® versus placebo was accomplished by evaluation of the second recording of the day 45 minutes after intake. Data from the first recording (baseline) were set to 100% and electrophysiological changes produced by placebo or PASCOFLAIR® were depicted as %-changes thereof.

Summary – Conclusions
Efficacy Results: The effectiveness of 2 tablets of PASCOFLAIR® was tested by using a new methodology called "EnkephaloVision", which consists of a combination of a fast quantitative EEG analysis termed "Neurocode- Tracking" and Eye-Tracking. Forty subjects suffering from test anxiety - selected by a questionnaire - were exposed to a series of mental tasks and emotional audio-visual video-clips before and 45 minutes after intake of 2 tablets of PASCOFLAIR®. After detection of a correlation between the questionnaire score values and measurement of absolute spectral EEG

power in the beta1 and beta2 range in fronto-temporal brain areas statistically significant increases of spectral beta1 and beta2 power were observed during 8 out of 10 of the challenges. Statistically highly significant increases of delta and theta power indicated strong mental activation during the challenges, especially during cognitive testing. Increases of beta waves during an identical scenery before and after intake of PASCOFLAIR® showing the disappearance of beta waves. Looking now at averaged data calculated over all electrodes and over two major brain areas (fronto-temporal and parieto-occipital), less spectral beta power is induced in general during the different cognitive and emotional challenges. Statistically conspicuous or significant attenuation was observed during the video-clips showing examination anxiety, showing emergency surgery and watching the horror video. Finally, all 102 parameters (17 electrode positions x 6 frequency ranges) were fed into a linear discriminant analysis for comparison with other drugs. The effect of PASCOFLAIR® (Verum) was projected at a considerable distance to the effect of its placebo proving its fast effectiveness within 45 min after intake. Comparing now the changes of spectral power in the presence of PASCOFLAIR® with the changes as observed in the presence of Placebo, clearly lower production of beta power was observed in nearly all challenges. As already detected in the correlation analysis mainly frontotemporal brain areas were involved plus the left parietal brain area represented by the electrode position P3. Increases in these areas have also been described in the presence of anxiety shortly before treatment at a dentist (Inaugural dissertation by Reuter J, to be published). Increase of beta waves in the temporal and frontal lobe of the brain has been also seen in earlier experiments during watching horror videos (Dimpfel, unpublished). The reduction of spectral power increases of beta waves can therefore be taken surely as a surrogate parameter for the anti-stress and calming effect of PASCOFLAIR®.

Safety Results: Tolerability and safety were excellent and no adverse events were detected in the presence of PASCOFLAIR®.

Conclusion: The fast begin of effectiveness defined as cerebral bioavailability of PASCOFLAIR® (within 30 minutes) has already been detected earlier (Dimpfel et al., 2012). In this earlier publication 3 tablets were administered. In the present investigation only 2 tablets were given and fast effectiveness confirmed at 45 minutes after intake. A further difference consisted in the fact that now subjects suffering from test anxiety were tested. Furthermore, the present study was performed using the new method "EnkephaloVision", which consists of a combination of a newly developed very fast EEG analysis called "Neurocode-Tracking" with Eye-Tracking. With the help of this advanced methodology a number of cognitive and emotional challenges were presented before and after intake of PASCOFLAIR® and evaluated scenery after scenery in a quantitative manner. A first important result was obtained by searching for a relationship between the questionnaire "Examination Anxiety" called "PAF" in this report and quantitative EEG changes in terms of spectral power. For the median over all electrodes of beta1 as well as of beta2 power a statistically significant correlation was found. This suggested a closer look at changes of beta waves in order to proof the efficacy of PASCOFLAIR®. A further precondition for this goal consisted in the question if the selected audio-visual challenges result in an increase of spectral beta power in comparison to just starring at a fixation cross on the screen. This was clearly the case, by it confirming that beta power should be selected as the target of quantitative EEG analysis in order to proof the efficacy of PASCOFLAIR®. Statistically significant increases of delta and theta power during most of the different challenges indicated a great mental activation. Frequency changes with respect to cognition are mainly observed in fronto-temporal brain areas, whereas frequency changes with respect to emotion are also seen in parieto-occipital regions. These areas are therefore looked at separately in terms of analyzing the action of PASCOFLAIR®. Comparing now the changes of spectral power in the presence of PASCOFLAIR® with the changes as observed in the presence of Placebo, clearly lower increases of beta power and a reduction of delta and theta power were observed in nearly all challenges. As already detected in the correlation analysis mainly fronto-temporal brain areas were involved plus the left parietal brain area represented by the electrode position P3. Increases in these areas have also been described in the presence of anxiety shortly before treatment at a dentist (Inaugural dissertation by Johanna Reuter, to be published). Increase

of beta waves in the temporal and frontal lobe of the brain has already been also seen in earlier experiments during watching horror videos (Dimpfel, unpublished). The reduction of spectral power increases of beta waves can therefore be taken surely as a surrogate parameter for the anti-stress and calming effect of PASCOFLAIR®. The fact that always the same fronto-temporal electrodes and P3 showed more or less statistically noticable or significant reductions in the beta range provides safe evidence that subjects experienced less stress and anxiety leading to higher focussing on the presented tasks. According to earlier preclinical investigations changes in beta1 power are related to glutamatergic neurotransmission (Dimpfel, 2015) whereas changes in beta2 frequencies are related to GABAergic transmission (Dimpfel, 2003). Due to the influence of PASCFLAIR® on beta activity its mechanism of action can be assumed to be related to changes of glutamatergic and GABAergic transmission, respectively. Interestingly, psychometric performance indicated no negative influence on cognitive function. Finally, discriminant analysis confirmed statistically the quick and potent effectiveness of PASCOFLAIR® in relation to other drugs or herbal preparations confirming and extending the data from the earlier publication.

References:

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