Section 2: The Exploration of Pharmacodynamic Effects To Identify Novel Indications
The effects of TPA023, a GABAA $\alpha_{2,3}$ subtype-selective partial agonist, on essential tremor in comparison with ethanol

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ABSTRACT

Background: Essential tremor (ET) is a relatively frequent neurological disorder that responds in about half the patients to non-selective GABA_A agonists (benzodiazepines). It is not known which GABA_A subtypes are involved in the therapeutic effects of benzodiazepines.

Methods: This double-blind, double-dummy, randomized, placebo-controlled, 3-period, crossover study was performed in nine ET patients with self-admitted tremor reduction after alcohol. The effects of TPA023 2 mg, a GABA_A (1,2,3 selective partial agonist, and an ethanol infusion (steady state concentration of 0.6 g·L⁻¹) on ET were investigated compared to placebo. Tremor evaluation included laboratory accelerometry and a performance-based scale. Additional Central Nervous System measurements were performed to evaluate other effects besides those on tremor.

Results: TPA023 was not effective in reducing tremor, while ethanol infusion diminished tremor in the postural and kinetic condition, as assessed by laboratory accelerometry. Ethanol did not affect tremor as assessed using the performance based scale. TPA023 decreased saccadic peak velocity, while ethanol infusion decreased VAS alertness.

Conclusions: This study showed that ethanol reduced maximum tremor power, as assessed by standard laboratory accelerometry, whereas TPA023 did not. These results suggest that the GABA_A (1,2,3-receptor is not important for the therapeutic effects of benzodiazepines on ET.
INTRODUCTION

Essential tremor (ET) is one of the most common movement disorders, affecting about 4% of the general population[1] and 5% in the age group above 65 years [2]. ET has a 4-12 Hz frequency that predominantly affects the upper extremities, may also affect the head and voice, and rarely affects the legs. In contrast to resting tremor in Parkinson disease, essential tremor is characterised by postural and kinetic components [3]. Although its cause is unknown, ET is attributed to a defect of central oscillatory systems at the level of the inferior olivary nucleus of the medulla oblongata [4]. Current therapy for ET includes beta blockers, primidone (a phenobarbital metabolite), benzodiazepines, and some antiepileptic agents. Treatment is symptomatic, effective in no more than roughly half of the patients, and often limited by side effects [5].

Preclinical and clinical studies suggest that a GABAergic pharmacologic agent could be effective in the treatment of ET [6]. A number of benzodiazepines are commonly used to treat patients with ET [5]. Double-blind studies have demonstrated efficacy of alprazolam versus placebo in treating ET [7,8]. Different GABA_A receptor subtypes have been identified, and preclinically linked to well-known effects of GABA_A agonists like sedation (α1) [9], muscle relaxation (α2) [10], anxiolysis (α2,3) [11,12] and memory impairment (α5) [13]. Among these subtypes, the α2-receptor seems the most promising target for anti-tremor activity, although the exact mechanism of the therapeutic activity of GABA agonists in essential tremor is unknown. TPA023 is being developed as a GABA_A α2,3 selective partial agonist. Based on the selective properties of this compound, it is believed to be a muscle relaxant (and anxiolytic) without causing sedation and instability. Healthy volunteer studies have shown the selective effect profile in comparison with lorazepam [14]. Investigating the effects of this novel selective partial GABA_A agonist on essential tremor might reveal new information about the pathophysiology of this disease, and possibly identify a new treatment modality.

Ethanol relieves tremor symptoms in an estimated 50 to 90% of ET patients[15,16] by reducing tremor amplitude without affecting frequency [17]. It most likely acts via a reduction of cerebellar over-activity, which results in reduced tremor amplitude, whereas the frequency remains unaffected [17-19]. In this study, ethanol was chosen as a positive control, which was delivered by intravenous infusion to maintain a blood ethanol concentration of 0.6 g·L⁻¹, using a novel clamping technique, based on earlier publications [20]. Since the duration of action of TPA023 was estimated to be four hours, the clamping procedure took place during a similar period. To maximize the power of ethanol as a positive control, only patients who were
familiar with the positive effects of ethanol on their symptoms were included in this project.

In the current study, the novel $\alpha_{2,3}$-selective GABA$_A$ partial agonist TPA023 was compared with intravenous ethanol and placebo for their effects on tremor symptoms. A battery of Central Nervous System (CNS) function tests including body sway, eye movements, Visual Analogue Scales and adaptive tracking was also performed. The objectives were to distinguish between general CNS pharmacodynamic effects of the GABA$_A$ $\alpha_{2,3}$-selective drugs and tremor-specific effects in the accelerometry recordings, in a relatively small study.

**METHODS**

Design

This study was a double-blind, double-dummy, randomized, placebo-controlled, 3-period, crossover study in nine patients diagnosed with essential tremor, with at least a five-day washout period.

Subjects

Nine patients with essential tremor were recruited from the hospital database of the Leiden University Medical Centre, the Dutch patients’ association and by advertising in local newspapers. Subjects were informed about the contents of the study during an information visit. When they had decided to participate, subjects visited the research unit for a medical screening. After signing informed consent, they were medically screened to evaluate eligibility for study participation. A neurologist diagnosed essential tremor (et) of the hands and forearms according to the diagnostic criteria for ‘classic et’ defined by the consensus statement of the Movement Disorder Society [21], adapted from previous criteria established by the Tremor Research Investigation Group (TRIG) [22], as well as a more recent study indicating the importance of kinetic tremor [23]. An isolated head tremor was not allowed.

Only subjects who stated a positive effect of ethanol on their tremor symptoms were included in the study. Subjects had to refrain from ethanol 48 hours prior to a treatment day and caffeine-containing products for at least 12 hours before treatment. Subjects were not allowed to use their own anti-tremor medications and had to abstain from grapefruit (juice) and St John’s Wort for at least 2 weeks before the start of the study until completion of the study. They were not allowed to drink more than six units of caffeine-containing products or three beverages of ethanol per day or smoke more than
five cigarettes per day during the total study period. On treatment days, the use of caffeine-containing products or smoking was not allowed. The study was approved by the Medical Ethics Review Board of Leiden University Medical Centre, and performed according to their standards.

Study treatments

Each patient received a single oral dose of TPA023 2 mg or matching placebo. Also on each study day, an ethanol (10% in 5% glucose) or sham placebo (5% glucose) clamping procedure was performed. Only the person who was responsible for the clamping method was unblinded for ethanol infusion due to measurement of the breath ethanol concentrations. This person was not involved in any other assessments.

To diminish variability due to changing ethanol levels, alcohol was infused using a recently developed clamping method [24]. Based on a procedure for clamping breath alcohol (BrAC) previously described by O’Connor [20], a spreadsheet-based ethanol clamping paradigm was developed. Changes in breath alcohol concentrations (BrAC) were used to adapt the intravenous infusion rate of ethanol (10% in 5% glucose). This results in pseudo-steady state ethanol levels with minimal variability [25]. An ethanol level of 0.6 g·L⁻¹ was chosen, because this was expected to cause a significant tremor reduction in the majority of patients without causing too many inadvertent effects. Previous studies have shown that mean blood alcohol levels of 0.35 and 0.50 g/L had tremor diminishing effects, but this was after a single oral dose [26].

In previous studies the 0.6 g·L⁻¹ ethanol clamp was well-tolerated and produced statistically significant pharmacodynamic CNS effects [24]. Considering its pharmacokinetic profile, it was estimated that the duration of action of TPA023 would be approximately four hours. To optimize the value of ethanol as a positive control, a clamping period of four hours was chosen for this study.

Safety

Adverse events, ECG, blood pressure and heart rate measurements were assessed throughout the study. ECGs were assessed with a Cardiofax, equipped with ecaps12 analysis program (Nihon Kohden, Japan). Blood pressure and heart rate were measured with an automated blood pressure monitor (MPV1072, Nihon Kohden, Japan), showing an average value for two sequential (duplicate) measurements at each time point. All safety measurements were made after sitting in a semi-recumbent position for at least 5 minutes.
Pharmacokinetics

Breath alcohol (BrAC) samples were performed using the hand-held Alco-Sensor IV meter (Honac, Apeldoorn, The Netherlands). To reduce fatiguing of the Alco-Sensor meter, a minimum interval of approximately 10 minutes was maintained between BrAC samplings, by alternating two different measurement devices. A recent study using the described ethanol clamping technique shows similar findings for breath alcohol and blood alcohol levels (data on file). Therefore, no pharmacokinetic blood samples were obtained for ethanol and only the breath alcohol samples were used for further pharmacokinetic analysis.

Pharmacodynamics

Tremor evaluation

Tremor evaluations were performed at screening, predose (within 60 minutes prior to dosing) and 60, 150, 240, 330, 420 minutes postdose on each study day.

At screening tremor was evaluated using the Tremor Disability Questionnaire to assess the level of disability due to ET according to the patients' opinion. This is a 36-item, 10 minute questionnaire that was designed in 1997 for the CADeT study [27]. It has shown substantial test-retest reliability and was validated against multiple other endpoints, including a neurologist's clinical ratings, the performance-based test of function, and quantitative computerized tremor analyses [28]. The total score of this questionnaire ranges from 0 (no disability) to 100 (completely disabled).

Additionally, a Performance-Based Tremor Evaluation was performed [29]. The test included the performance of 15 activities that were scored by a trained measurement assistant from 0 (no difficulty) to 4 (unable to perform), and the total score was converted to a percentage that ranges from 0 (no disability) to 100 (maximally impaired) [29].

Laboratory tremography Tremor was evaluated according the methodology of Gironell et al. [30] using three miniature linear piezo-electric accelerometers (Nihon Kohden, MT-3T), which were attached to the distal end of a clamp, above the fingertips of the dominant arm. The accelerometers were placed at right angles to one another to enable three-dimensional analysis of movement [30,31]. An EMG recording of the flexor and extensor forearm muscles was...
also obtained with silver-silver chloride electrodes applied 2cm apart at the belly of the muscles. The signals were amplified by use of a Grass 15LT (15A54/15A94), with a time constant of 1 second and a low pass filter at 100 Hz. For the fast Fourier analysis, data collection and analysis were performed using customised CED software (Cambridge Electronics Design, Cambridge, UK). The upper limb tremor was recorded in three positions, each held for a 60-second interval: (1) at rest, with the arm hanging relaxed along the body, (2) postural, with the arm held in an outstretched, horizontal, prone position and (3) kinetic, moving the hand from a set point to the nose (back and forth). Tremor was quantified by a power spectrum analysis to determine the dominant frequency peak (Hz) and the magnitude of the accelerometer signal (absolute power of the dominant frequency peak in μV).

**CNS measurements**

Pharmacodynamic measurements were performed predose (within 60 minutes prior to dosing) and 30, 120, 210, 300, 390 and 480 minutes postdose. Subjects underwent pharmacodynamic tests individually in a quiet room with ambient illumination. All subjects were thoroughly trained and familiarized with the tests within 14 days preceding study start to minimize learning effects before proceeding to the study.

**Saccadic eye movements**

Saccadic eye movements were recorded using a micro-computer-based system for data recording (Cambridge Electronics Design, Cambridge, UK), Nihon Kohden equipment for stimulus display, signal collection and amplification (Nihon Kohden Corporation, Tokyo, Japan), and disposable surface electrodes (Medicotest n-o-s, Olbykke, Denmark) [[32]]. Average values of latency (= reaction time), peak saccadic velocity and inaccuracy (difference between stimulus angle and corresponding saccade in %) were calculated for all artefact free saccades. Saccadic peak velocity (SPV) has been validated as the most sensitive measure for the sedative effects of benzodiazepines [[33-36]]. Previous healthy volunteer studies showed that TPA023 caused SPV reductions, while ethanol did not [[14,24]].

**Visual analogue scales**

Visual analogue scales as originally described by Norris [[37]] were previously used to quantify subjective effects of benzodiazepines [[33]] From the set of sixteen scales three composite factors were derived as described by Bond and Lader [[38]], corresponding to alertness, mood and calmness. These factors were used to quantify subjective treatment effects. In contrast to TPA023, ethanol has previously shown to affect the VAS alertness scale [[14,24]].
Body sway was measured with an apparatus similar to the Wright ataxia meter [39], which integrates the amplitude of unidirectional body movement transferred through a string attached to the subject’s waist. Two-minute measurements were made in the antero-posterior direction with eyes closed, with subjects standing comfortably on a firm surface with their feet slightly apart. In contrast to tPA023, ethanol has previously shown to increase postural instability [14, 24].

Adaptive tracking The adaptive tracking test was first performed by Borland and Nicholson [40], using customised equipment and software (Hobbs, 2000, Hertfordshire, UK). The average performance and the standard deviation of scores were used for analysis. Adaptive tracking is a pursuit-tracking task. A circle moves randomly about a screen. The subject must try to keep a dot inside the moving circle by operating a joystick. If this effort is successful, the speed of the moving circle increases. Conversely, the velocity is reduced if the test subject cannot maintain the dot inside the circle. Adaptive tracking was scored over a 3-minute period. Each test was preceded by a run-in period. The adaptive tracking test has proved to be useful for measurement of CNS effects of ethanol [41], various psychoactive drugs [42], and sleep deprivation [35].

Statistical analyses
Most PD parameters were analyzed by mixed model analyses of variance (using SAS PROC MIXED) with treatment, period, time and treatment by time as fixed effects, with subject, subject by time and subject by treatment as random effects, and with the baseline value as covariate, where baseline is defined as the average of the available values obtained prior to dosing. Treatment effects were reported as the contrasts specified below where the average of all post-dose measurements was calculated within the statistical model. Contrasts were reported along with 95% confidence intervals (95%CI) and analyses were two-sided with a significance level of 0.05.

Body sway and tremor parameters were analyzed after log-transformation due to skewed response distribution. All other parameters were analyzed untransformed. Log-transformed parameters were back-transformed after analysis where the results may be interpreted as percentage change.

All calculations were performed using SAS V9.1.2 for Windows (SAS Institute, Inc., Cary, NC, USA).
RESULTS

Subjects
Seventeen patients were medically screened after giving written informed consent. Seven patients did not qualify for the study mainly because of a too mild tremor that could not be measured with the laboratory tremography. Nine patients (two female, seven male) fulfilled the study criteria and entered and completed the study. Apart from their tremor, they were judged to be in good health on the basis of medical history, physical examination and routine laboratory data. Subjects were on average 47 years of age (range 18-80), had an average weight of 77 kg (range 62-103 kg) and average height of 175 cm (range 159-189 cm).

The mean (range) dominant tremor frequency at screening was 7.7 (95%CI 5.4-9.4) Hz. Mean (Standard Deviation) scores on the Tremor Disability Questionnaire and Performance-Based Tremor Evaluation were 30 (18.2)% and 34 (30)% respectively. Two patients stopped their propranolol treatment two weeks before participation in this trial. The other patients did not use any treatment.

Clinical observations
No serious adverse reactions occurred following any of the treatments. Frequently reported adverse events include headache, sleepiness, dizziness and a painful arm during infusion. Headache was the most common adverse event, occurring in five, one and two patient(s) after administration of ethanol, TPA023 and placebo, respectively. Dizziness and sleepiness occurred in four, two and one subject(s) after administration of ethanol, TPA023 and placebo, respectively. Five patients reported a painful arm just after the start of the ethanol infusion. All adverse events were single occasions and considered mild of intensity.

Pharmcodynamics
Tremor evaluation
LABORATORY TREMOGRAPHY During the postural condition of the measurement, ethanol infusion reduced maximum power of both the left-right (-31.4% (-45.9, -13.0%)) and backward-forward (-37.6% (-60.4, -1.7%)) tremor direction compared to placebo. For the kinetic condition, similar results were obtained (table 1). The maximum power of the left-right direction was reduced with 19.2% (-31.7, -4.3%) and that of the backward-forward direction with 29.5% (-44.8, -9.9%).
after ethanol infusion compared to placebo. These changes have resulted in a decrease in average power in both conditions. In the resting condition, no effects were seen in any tremor direction for any treatment.

**Performance-Based Tremor Evaluation** Mean total tremor score decreased shortly after ethanol infusion had begun (figure 3). However, mean scores during placebo and TPA023 treatment also decreased. No differences compared to placebo were present after ethanol (-2.2 [-6.3, 1.9]) and TPA023 (-1.0 [-5.1, 3.0]) treatment (table 1).

**Central Nervous System Tests**

*Saccadic Eye Movements* TPA023 significantly decreased saccadic peak velocity (SPV) with 45.4 deg/sec (-65.6, -25.1 deg/sec) compared to placebo. TPA023 also increased inaccuracy with 1.0% (0.3, 1.6) but not latency. Ethanol did not show any effects on eye movements (table 2).

*Body Sway* Neither of the treatments significantly affected body sway compared to placebo (table 2).

*Adaptive Tracking* Adaptive tracking performance and SD of performance were not significantly affected compared to placebo (table 2).

*Visual Analogue Scales* Ethanol decreased the VAS alertness scale with 8.0 mm (-13.2, -2.7 mm) compared to placebo. VAS mood and VAS calmness were not affected significantly by ethanol or TPA023 treatment (table 2).

**Pharmacokinetics**

Mean breath ethanol concentrations increased in approximately 15 minutes to 0.58 g/L and stabilized for 4 hours, after which the infusion was stopped and concentrations returned to baseline (figure 1).

**Discussion**

This placebo-controlled study investigated the effects of a novel GABA<sub>A</sub> α2,3 selective partial agonist in patients with essential tremor. Results showed that only ethanol, which was used as a positive control, reduced tremor power, as assessed by the laboratory tremography. Several studies have shown that ethanol is effective in reducing tremor amplitude in patients with essential tremor [15,17,26,43]. It is thought...
that ethanol acts within the central nervous system and not by affecting peripheral tremorogenic mechanisms \[26,43\]. Previous studies included a single oral intake of ethanol or an infusion bolus, causing mean blood ethanol levels of 0.035-0.055 g/dL \[26\]. These studies showed that these levels affected tremor. The current study was able to keep ethanol levels stable at 0.6 g/L for approximately four hours. Tremor power was reduced as long as the ethanol levels were stable and returned to baseline after infusion was stopped.

TPAO23 treatment did not show any effects compared to placebo. It is unlikely that this was due to doses that were too low. There were clear effects of TPA023 on saccadic eye movements in this study. The dose was predicted to be therapeutically active for the treatment of anxiety. A positron emission tomography study (MSD, data on file) demonstrated that the dose of TPA023 used in this study (2.0 mg ionizing radiation) shows substantial and sustained occupancy (47 to 64\% at ~2 hours and 34 to 59\% at ~7 hours postdosing). Although the required receptor occupancy for the postulated GABAergic effect in ET is unknown, these levels are consistent with the occupancy associated with the minimum effective dose in animal models of anxiolysis (44 to 76\%, 46\%, and 89\%, for the elevated plus maze, fear-potentiated startle and conditioned suppression/drink paradigm, respectively), indicating that they are likely to be centrally active. In addition, the preliminary results of a fear-potentiated startle paradigm in healthy subjects support the anxiolytic efficacy of single dose TPA023 2.0 mg (MSD, data on file). In that study, startle amplitude during threat conditions was significantly reduced when subjects received TPA023 2.0 mg compared to placebo (p<0.0035).

To maximize the power of ethanol as a positive control, only patients who were familiar with the positive effects of ethanol on their symptoms were included in this project. Since ET may be etiologically heterogeneous, a response to ethanol (which acts as an allosteric GABA\_A agonist) was also expected to increase the chance of finding effects with a subtype-selective GABA\_A agonist. Patients were not evaluated for (prior) responses to benzodiazepines or barbiturates, because clinical efficacy was expected to be influenced by a mixture of (lack of) tremor reduction and (unacceptable) side effects. Thus, the clinical response to full GABA-agonists could not a priori be used to predict the effects of a subtype-selective partial GABA\_A agonist.

For treatment of ET and anxiety, similar clinical doses of benzodiazepines are used [1,44]. Therefore, the lack of effects of TPA023, which has a selective activity at the α2,3 subunit of the GABA\_A receptor, suggests that effects of GABAergic treatments of tremor are not mediated via the α2,3 subunit. It is uncertain which other GABA\_A receptor subtypes are involved. The α5 subunit is mainly located in
the hippocampus, and it has been involved in memory processes [27]. The α1 subunit is probably the best candidate, since it is the most widely distributed GABA<sub>Α</sub> receptor subtype [45]. Recently, the α1 subunit knockout mouse has been introduced as an animal model for essential tremor as it exhibits postural and kinetic tremors that clearly reproduce the features of essential tremors [46,47]. This suggests that the expression of α1 subunits in the brains of patients with ET may be abnormal. A pilot study in ET patients, however, could not demonstrate any relation between ET and variants in the gene coding for this α1 subtype receptor [48]. Nevertheless, other defects in the α1 subunit may still play a role in the pathophysiology of ET. Since this receptor subtype is also involved in sedation, it may be difficult to find GABAergic tremor treatment that is completely devoid of this side effect, which is particularly cumbersome in elderly patients.

It appeared that tremor power was largely reduced in all treatment groups in the first hour after treatment had started, as shown in figure 2. After this initial decrease, tremor remained stable during placebo treatment. This suggests that tremor was enhanced at baseline, e.g. by stress associated with the start of the study day [49], or that there is a substantial initial placebo effect in treating ET. The ethanol effects were still clearly present on top of these significant placebo effects. Nonetheless, a wash-in placebo infusion would be useful in future studies, to ensure a reduction to stable baseline tremor levels in this patient group.

Although clinical rating scales have proven their effectiveness in the assessment of ET severity [50,51], the performance-based tremor evaluation scale used in this study was not able to measure a statistically significant effect of ethanol on ET, compared to placebo. The scoring of the test was performed by four trained persons, which might have caused too much inter-rater variability to detect a significant effect in this small study.

In healthy volunteers, ethanol causes readily detectable increases in body sway and decreases in adaptive tracking [24], but this could not be found in our study. This could have been caused by two opposing effects of ethanol in this patient group. On the one hand, ethanol has positive effects on the tremor itself, counterbalancing the negative performance on this task caused by alcohol [24]. Similar factors could play a role in the lack of effects on body sway. Previous studies have shown that patients with essential tremor had higher baseline ataxia scores compared to healthy controls, which diminished after alcohol ingestion [52]. As for general performance, the lack of a net effect of ethanol on body sway could be explained by a reduction of ataxia in ET, combined with ethanol-induced postural instability. This might be a reason for the difference of ethanol effects between healthy volunteers and this patient group.
This study has shown that treatment with an $\alpha_{2,3}$ subunit selective GABA$_A$ partial agonist was not effective for the treatment of essential tremor. This suggests that the $\alpha_{2,3}$ subunit of the GABA$_A$ receptor is not involved in the pathophysiology of essential tremor or in the beneficial effects of non-selective benzodiazepines. Additionally, the study has shown that the methodology of ethanol infusion can be well used as a positive control in studies with patients with essential tremor.
Table 1  Effects on tremor. Least Square Means and treatment differences relative to baseline for different tremor variables ANOVA results are shown as contrasts (%), p-values and 95% CI.

<table>
<thead>
<tr>
<th>Laboratory accelerometer maximum power variables</th>
<th>TPA023 - Ethanol</th>
<th>Placebo</th>
<th>TPA023 - Placebo</th>
<th>Ethanol - Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up-Down (uV)</td>
<td>0.192</td>
<td>0.149</td>
<td>0.151</td>
<td>-2.2,</td>
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<tr>
<td>Left-Right (uV)</td>
<td>0.316</td>
<td>0.263</td>
<td>0.289</td>
<td>-18.8,</td>
</tr>
<tr>
<td>Back-Forward (uV)</td>
<td>0.174</td>
<td>0.150</td>
<td>0.139</td>
<td>-6.8,</td>
</tr>
<tr>
<td>Average Maximum power (uV)</td>
<td>0.233</td>
<td>0.191</td>
<td>0.195</td>
<td>-13.4,</td>
</tr>
<tr>
<td>Postural</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Up-Down (uV)</td>
<td>0.623</td>
<td>0.390</td>
<td>0.588</td>
<td>-31.2,</td>
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<tr>
<td>Left-Right (uV)</td>
<td>0.782</td>
<td>0.495</td>
<td>0.721</td>
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</tr>
<tr>
<td>Back-Forward (uV)</td>
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<td>0.317</td>
<td>0.508</td>
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<tr>
<td>Average Maximum power (uV)</td>
<td>0.652</td>
<td>0.416</td>
<td>0.620</td>
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<td>Kinetic</td>
<td></td>
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<tr>
<td>Up-Down (uV)</td>
<td>1.296</td>
<td>1.108</td>
<td>1.393</td>
<td>-6.9,</td>
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<tr>
<td>Left-Right (uV)</td>
<td>2.719</td>
<td>2.344</td>
<td>2.899</td>
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<tr>
<td>Back-Forward (uV)</td>
<td>1.112</td>
<td>0.866</td>
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<tr>
<td>Average Maximum power (uV)</td>
<td>1.741</td>
<td>1.486</td>
<td>1.862</td>
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<tr>
<td>Performance Based Tremor Evaluation score</td>
<td>15.1</td>
<td>13.9</td>
<td>16.1</td>
<td>-1.0,</td>
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### Pharmacodynamic effects

Least Square Means and pharmacodynamic differences relative to baseline for Saccadic Eye Movements, Visual Analogue Scales, Body Sway and Adaptive Tracking. ANOVA results are shown as contrasts, p-values and 95% CI.

<table>
<thead>
<tr>
<th>CNS Variable</th>
<th>LS Means TPA023</th>
<th>Ethanol</th>
<th>Placebo</th>
<th>Ethanol - Placebo</th>
<th>P-value</th>
<th>95% CI</th>
<th>P-value</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Saccadic Peak Velocity (deg/sec)</td>
<td>4.136</td>
<td>4.432</td>
<td>4.590</td>
<td>-0.454</td>
<td>0.0002</td>
<td>-5.6</td>
<td>-0.003</td>
<td>-5.3</td>
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<td>latency (sec)</td>
<td>0.233</td>
<td>0.228</td>
<td>0.224</td>
<td>0.09</td>
<td>0.14</td>
<td>0.002</td>
<td>0.021</td>
<td>0.004</td>
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<tr>
<td>Inaccuracy (%)</td>
<td>7.5</td>
<td>6.5</td>
<td>6.6</td>
<td>1.0</td>
<td>0.0002</td>
<td>0.5</td>
<td>1.6</td>
<td>0.008</td>
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<tr>
<td>vas Alertness (mm)</td>
<td>6.16</td>
<td>56.2</td>
<td>64.2</td>
<td>-2.6</td>
<td>0.33</td>
<td>9.1</td>
<td>2.9</td>
<td>0.065</td>
</tr>
<tr>
<td>vas mood (mm)</td>
<td>73.8</td>
<td>73.2</td>
<td>73.0</td>
<td>0.2</td>
<td>0.02</td>
<td>9.0</td>
<td>3.6</td>
<td>0.7</td>
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<tr>
<td>vas Calmness (mm)</td>
<td>6.45</td>
<td>6.9</td>
<td>6.1</td>
<td>3.6</td>
<td>0.24</td>
<td>10.0</td>
<td>2.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Body Sway Eyes Closed (mm)</td>
<td>14.6</td>
<td>14.01</td>
<td>15.03</td>
<td>-1.43</td>
<td>0.065</td>
<td>2.96</td>
<td>0.10</td>
<td>1.02</td>
</tr>
<tr>
<td>Adaptive tracking performance</td>
<td>1.47</td>
<td>2.61</td>
<td>3.53</td>
<td>-0.06</td>
<td>0.71</td>
<td>-0.37</td>
<td>0.26</td>
<td>0.09</td>
</tr>
<tr>
<td>SD of adaptive tracking performance</td>
<td>0.47</td>
<td>0.61</td>
<td>0.53</td>
<td>0.00</td>
<td>0.54</td>
<td>0.22</td>
<td>0.40</td>
<td>0.09</td>
</tr>
</tbody>
</table>
Figure 1  Average graph of breath alcohol concentrations (g/L) with SD error bars. Maximum and minimum values are shown with thin lines.
Figure 2  Graphs show changes from baseline of average maximum power of laboratory accelerometry in postural and kinetic condition with 95% CI error bars. Closed circle is TPA023, square is ethanol, open circle is placebo.
**Figure 3** Graph shows change from baseline of average score on performance-based tremor evaluation scale with 95% CI error bars. Closed circle is TPA023, square is ethanol, open circle is placebo.
REFERENCES

37 Wright BM. A simple mechanical ataxia-meter. J Physiol 1951; 118: 27P-28P.