The pharmacokinetic and pharmacodynamic effects of \textit{SL65.1498}, a GABA\textsubscript{A} \textalpha{}2,3 selective agonist, in comparison with lorazepam in healthy volunteers

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Benzodiazepines are effective short-term treatments for anxiety disorders, but their use is limited by undesirable side-effects related to central nervous system (CNS) impairment and tolerance development. SL65.1498 is a new compound that acts in vitro as a full agonist at the \textit{GABA}_A \alpha_2 and \alpha_3 receptor and as a partial agonist at the \alpha_1 and \alpha_5 receptor-subtype. It is thought that the compound could be anxiolytic by its activation at the \alpha_2 and \alpha_3 receptor subtypes, without causing unfavourable side effects, which are believed to be mediated by the \alpha_1 and \alpha_5 subtypes. This study was a double-blind, five way cross-over study to investigate the effects of three doses of SL65.1498 in comparison to placebo and lorazepam 2 mg in healthy volunteers. The objective was to select a dose level (expected to be therapeutically active), free of any significant deleterious effect. Psychomotor and cognitive effects were measured using a validated battery of measurements, including eye movements, body sway, memory tests, reaction time assessments and visual analogue scales (VAS).

The highest dose of SL65.1498 showed small effects on saccadic peak velocity and smooth pursuit performance, although to a much lesser extent than lorazepam. In contrast to lorazepam, none of the SL65.1498 doses affected body sway, VAS alertness, attention or memory tests.

This study showed that the three doses of SL65.1498 were well tolerated and induced no impairments on memory, sedation and psychomotor and cognitive functions.
**INTRODUCTION**

In the 1960s, benzodiazepines were considered the gold standard for treatment of anxiety and various phobias. Although they seemed the perfect drugs, based on their rapid onset of efficacy, they have become less favourable for prolonged therapy, due to their propensity for development of tolerance and dependency, and their adverse side-effect profile related to central nervous system (CNS) impairment. These side effects are caused by the non-selective binding profile of the full agonists to the different $\text{GABA}_A$ receptor subtypes. Several pre-clinical studies have shown that stimulation of receptors containing subunits are associated with anxiolysis \cite{1,2}. Receptors with $\alpha_1$ subunits are thought to be responsible for sedation, and the $\alpha_5$ subtype for memory. Therefore, new compounds have been developed that are more selective agonists for the $\text{GABA}_A$ $\alpha_{2,3}$ subtype receptors, and are antagonists or partial agonists at $\alpha_1$ and $\alpha_5$ subtypes. This should result in an anxiolytic compound with less of the unwanted side effects that existing benzodiazepines possess.

$\text{S}1\text{65.1498}$ is a full agonist at receptors containing $\alpha_2$ and $\alpha_3$ subunits with an efficacy of 115 and 83\% respectively, relative to a full agonist. It is a partial agonist at those containing $\alpha_1$ and $\alpha_5$, showing a relative efficacy of 45 and 50\%, respectively \cite{3}. Behavioural studies in rodents demonstrated that $\text{S}1\text{65.1498}$ elicited similar anxiolytic-like activity to that of diazepam \cite{3,4}. Other effects like muscle weakness, ataxia, and sedation were also induced but at much higher doses than those producing anxiolytic-like effects. In non-human primates, $\text{S}1\text{65.1498}$ also showed anxiolytic-like (anti-conflict) effects as assessed by a conditioned conflict test model, without showing sedation \cite{5}. For the current study, three doses of $\text{S}1\text{65.1498}$ were selected that produced plasma concentrations in Phase I studies, which were predicted to be in the therapeutic range. At these plasma concentrations, animal studies showed potent anxiolytic-like activity similar to that of benzodiazepines, without any sedative effects \cite{3,4}.

To determine the psychopharmacological profile of these three doses, they were investigated using a validated battery of Central Nervous System (CNS) measurements in comparison to the effects of lorazepam and placebo. The measurements included saccadic eye movements, smooth pursuit, body sway, visual analogue scales and memory, cognition and attention tests. Previous studies have shown that benzodiazepines significantly decrease saccadic peak velocity, postural stability and memory \cite{6-11}. The objective was to identify a dose level that was expected to be in the therapeutic range and that was free of any clinically significant deleterious effect compared to placebo.
METHODS

Design
This study was a placebo controlled, randomised, double-blind, five-way, cross-over, single-centre study in twenty healthy male volunteers, with a washout period between 7 and 14 days.

Subjects
Twenty healthy male and female volunteers were recruited from the chdr database. All volunteers gave written informed consent and were medically screened before entry to the study. Subjects were not allowed to smoke more than five cigarettes per day and had to refrain from smoking during the study day. They were asked not to drink alcohol 48 hours prior to and 24 hours following a study day and to refrain from drinking xanthine-based and grapefruit-containing products from 24 hours before until the end of the study day. The use of medication or products containing St John’s Wort was not allowed during the study period. The study was approved by the Medical Ethics Review Board of Leiden University medical Centre.

Treatments
On randomized treatment days, each subject received a single oral dose of sl65.1498-00 2.5 mg, 7.5 mg, 25 mg, lorazepam 2 mg (2*1 mg) or placebo administered with 250 ml of water in a fasted state in the morning. All treatments looked identical and consisted of 2 capsules. Lorazepam and placebo tablets were enclosed in capsules for blinding purposes. The treatment sequences were determined using 5x5 Williams design with two subjects per sequence.

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), which displays an average value for two sequential (duplicate) measurements at each time point. All ECG, blood pressure and heart rate measurements were made after the subject had been sitting in a semi-recumbent position for at least 10 minutes.
Pharmacokinetics

Blood samples (7 ml) were drawn on each treatment occasion within 1 hour predose and 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 24 and 48 hours postdose to obtain plasma for assay of SL65.1498 and lorazepam concentrations.

Plasma was separated from heparinized blood samples by centrifugation (2000 g, 10 min, 4°C) to 3.6 ml Nunc cryotubes and stored at -20°C within 30 minutes after sampling. SL65.1498 analysis was accomplished using an Atmospheric Pressure Chemical Ionisation validated LC-MS/MS method. The quantitation limit of the assay was 0.5 ng/mL. Assays were performed in the Department of Clinical Metabolism and Pharmacokinetics at Sanofi-Aventis Research, Alnwick, Northumberland, UK.

A LC-MS/MS method using positive ion Turbo Ionspray with multiple monitoring (mrm) was validated for the quantification of lorazepam in human plasma. The calibration curves of lorazepam were linear between 0.500 and 50.0 ng/mL in human plasma and the limit of quantification (loq) was 0.500 ng/mL. Assays were performed by Ppd Development, Richmond, Virginia, USA.

Pharmacodynamics

Pharmacodynamic measurements were performed predose (within 30 minutes prior to dosing) and 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, and 10 hours postdose. Pharmacodynamic tests were performed in a quiet room with ambient illumination with only 1 subject in the same room per session. Each session consisted of the following sequence of tests: body sway eyes closed VAS saccadic eye movements. Cognitive function tests were performed at fixed times within the 2-4 hours-postdose period between the other measurements. All subjects were thoroughly trained and familiarized with the psychometric tests within 7 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-00-S, Olstykke, Denmark) [12]. Saccadic peak velocity has been validated as the most sensitive measure for the sedative effects of benzodiazepines [6-8].
Smooth Pursuit

The same system as used for saccadic eye movements was also used for measurement of smooth pursuit. For smooth pursuit eye movements, the target moves sinusoidally at frequencies ranging from 0.3 to 1.1 Hz, by steps of 0.1 Hz. The amplitude of target displacement corresponds to 20 degrees eyeball rotation to both sides. Four cycles were recorded for each stimulus frequency. The method has been validated at CHDR by Van Steveninck et al. [12] based on the work of Bittencout et al. [13] and the original description of Baloh [14]. The time in which the eyes were in smooth pursuit of the target was calculated for each frequency and expressed as a percentage of stimulus duration. The average percentage of smooth pursuit for all stimulus frequencies was the parameter used.

Visual Analogue Scale

Visual analogue scales as originally described by Norris [15] were previously used to quantify subjective effects of benzodiazepines [7]. From the set of sixteen scales three composite factors were derived as described by Bond and Lader [16], corresponding to alertness, contentedness and calmness. These factors were used to quantify subjective drug effects.

Body Sway

Body sway was measured with an apparatus similar to the Wright ataximeter [17], which integrates the amplitude of unidirectional body movements 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. Body sway is a measure of postural stability that has previously been shown to be sensitive to benzodiazepines [18].

Cognitive Function Tests

Memory testing was performed using the validated Eprime program [19,20]. At 2 hours post-dose, subjects were presented 30 words in three consecutive word trials (word learning test). Each trial ended with a free recall of the presented words (Immediate Recall). Approximately thirty minutes after start of the first trial, the volunteers were asked to recall as many words as possible (Delayed Recall). Immediately thereafter, the volunteers underwent the delayed memory recognition test, which consisted of 15 presented words.
and 15 ‘distractors’ (Delayed Recognition). At 3 hours post-dose, when the subjects were presented with 14 abstract visual patterns for 3 seconds. Hereafter, the same visual patterns were presented along side a ‘distractor’. Subjects were then asked to indicate which visual pattern was previously presented. This testing was repeated 30 minutes later. Word and picture recognition and recall tests were performed to assess reaction time and number of correct and incorrect answers. The Corsi block tapping test, constructed according the principles of the original Corsi block tapping task [21], assessed the nonverbal memory span. The visual and auditory reaction times tests were performed using the validated FePsy program (The Iron Psyche) [22,23].

Memory tests have been shown to be affected by benzodiazepines [9,10].

Analysis

Pharmacokinetics

Pharmacokinetics of 565.1498 were determined using a non-compartmental analysis model. Parameters determined were maximum plasma concentrations, time to maximum plasma concentration, $\text{auc}$, apparent clearance (clearance divided by bioavailability) and elimination half-life. Estimation was performed using WinNonlin software (WinNonlin Network Version 3.1, Pharsight, Cary, NC, USA).

Statistics

Treatment response was characterised for continuously measured variables by calculating the area under the effect curve ($\text{auec}$) relative to baseline over 6 hours. The pre-values were averaged and set at time $= 0$ hr. Change from average pre-value (delta) was calculated. The $\text{auec}$s were calculated using the linear trapezoidal rule up to 6 hours on the basis of protocol (planned) time points and were subsequently divided by the corresponding time span resulting in weighted average change from pre-value. All variables were analysed untransformed.

As cognitive function test results were assessed only once for each treatment, raw scores were analysed. Statistical analysis was initially performed using analysis of variance with factors treatment (4 levels) subject (12 levels) occasion (4 levels) and carry-over (5 levels, coded as the treatment preceding the current treatment, including ‘no preceding treatment’). If the carry-over effect was found to be non-significant, the analysis was rerun without the carry-over factor. The
four treatments were compared within the ANOVA model using the following contrasts: placebo - SL65.1498 2.5 mg, placebo - SL65.1498 7.5 mg, lorazepam 2 mg - SL65.1498 25 mg and placebo - lorazepam 2 mg. Overall p-value for the treatment effect was reported along with the specified contrasts with 95% confidence intervals and p-values.

With 20 subjects, there was 95% power to detect a SPV-reduction of at least 35 degree/sec/h after SL65.1498 treatment when compared with placebo in aueo-6h saccadic peak velocity, assuming the within-subject SD equal to 30 degree/sec/h.

RESULTS

Subjects

Eleven male and eleven female subjects were medically screened after giving written informed consent and ten of each group completed the study. Subjects were on average 25 years of age (range 19-38), had an average weight of 74 kg (range 58-98 kg) and average height of 175 cm (range 163-191 cm).

Clinical observations

No serious adverse reactions occurred following any of the treatments. The most frequently reported adverse event was sedation, which was reported in the lorazepam (fourteen subjects), SL65.1498 2.5 mg (six subjects), SL65.1498 7.5 mg (three subjects), SL65.1498 25 mg (eight subjects) and placebo group (seven subjects). Another reported adverse event was dizziness which was reported by nine subjects in the lorazepam group and one subject each in the placebo, SL65.1498 7.5 mg and 25 mg groups.

Pharmacokinetics

The mean (SD) plasma concentration-time curves for the three doses of SL65.1498 are shown in figure 1. All doses of SL65.1498 showed maximum concentrations between 3.01 and 3.75 hours. The mean C_MAX X (SD) was dose-proportional at 375 (129) ng/mL for the highest dose, 126 (40.1) for the middle and 37.3 (12.7) for the lowest. Elimination half-life was 11.0 (2.9) h, 10.7 (2.9) and 12.2 (3.4) h for SL65.1498 25, 7.5 mg and 2.5 mg respectively.

Lorazepam 2 mg showed maximum concentrations between 0.50 and 3.50 h with a mean (SD) C_MAX of 22.8 (5.1) ng/mL. Elimination half-life (SD) was 17.3 (4.3) h. These pharmacokinetic properties of lorazepam were in agreement with published data [24,25].
Pharmacodynamics

Saccadic Eye Movements
Lorazepam 2 mg and s165.1498 25 mg decreased Saccadic Peak Velocity (SPV) compared with placebo (decreases in AUC 0-6hr 45.7 deg/sec and 15.0 deg/sec respectively (Table 1)). The lower doses of s165.1498 doses did not affect the eye movements significantly (table 1, figure 2).

Smooth Pursuit
Lorazepam and to a lesser extent s165.1498 25 mg decreased smooth pursuit performance compared with placebo, while the other two doses of s165.1498 did not affect this parameter (table 1, figure 3).

Visual Analogue Scale
Only lorazepam caused effects on VAS alertness (Figure 4) and VAS contentedness compared with placebo, while none of the s165.1498 doses caused changes in any VAS subscale (table 1).

Body Sway
Body sway was only affected by lorazepam compared with placebo and not by one of the three doses of s165.1498 (table 1, figure 5).

Cognitive Function Tests and Corsi Block Tapping Task
During the learning phase of word recall test, the mean number of correct responses increased from the first to the third test in all treatment groups. Lorazepam decreased the number of correct responses in both the immediate and delayed word recall test, while responses after each dose of s165.1498 were comparable with responses after placebo treatment (table 2). The number of correct responses for the delayed word recognition test was comparable between placebo and s165.1498 treatment. Lorazepam decreased this number by 6.1 words compared with placebo (table 2).

The number of correct responses of the immediate/delayed picture recognition was similar between all study groups (results not shown).

The mean latency of correct responses after the simple auditory and visual reaction time test was increased after lorazepam administration (table 3). Results for the dominant and non-dominant hand (results not shown) were comparable.
For the binary choice reaction time test, there was no difference in mean number of correct responses between study treatments and placebo (table 3)

**DISCUSSION**

This study investigated the effects on CNS measurements of three doses of a new GABA<sub>A</sub> subtype selective agonist, SL65.1498, and compared these with the effects of a full GABA<sub>A</sub> agonist and placebo in healthy volunteers. The main aim was to determine whether SL65.1498 was free of deleterious effects at a dose level that was expected to be therapeutically active, based on animal models [3,4]. It was compared with lorazepam 2 mg, which is known to be a therapeutically relevant dose [26,27].

This study showed that the three doses of SL65.1498 induced no impairments on memory, subjective alertness and psychomotor and cognitive functions. Only the highest dose of SL65.1498 showed effects on saccadic peak velocity (SPV) and smooth pursuit performance, although much less than lorazepam. In this respect, the aim of the study was achieved as even the highest dose did not show clinically significant deleterious effects compared to placebo. The lack of effects on memory, body sway, attention and vas alertness could mean a more favourable side effect profile compared to the commonly used benzodiazepines. The only significant effects of the highest dose of SL65.1498 were on eye movements. The reductions in SPV and smooth pursuit were only about one third of the effects of lorazepam. SPV reduction has been shown to be a quite sensitive biomarker for sedation caused by several different CNS-depressants, including GABAergic [7,8], histaminergic (H1) [28] and noradrenergic [29] or physiological conditions [6]. The limited SPV-decrease of 15 deg/sec with SL65.1498 25 mg is probably still compatible with the lack of subjective sedation [6]. However, a recently published review indicated that a reduction in SPV is also quantitatively associated with the anxiolytic effects of benzodiazepines [11]. Since the effects on SPV are very low in comparison to those of lorazepam 2 mg or other anxiolytic benzodiazepines in the literature [11], this may imply that SL65.1498 25 mg not only has a lower sedative propensity, but also a lower anxiolytic efficacy. Recently, two other partial subtype-selective GABA<sub>A</sub> agonists showed SPV-reductions that were quite similar to lorazepam, hence much larger than for SL65.1498 [9,30]. These compounds had hardly any other CNS-effects, indicating that significant SPV-reductions can occur without reductions of alertness. It remains to be seen whether this translates into anxiolysis without sedation. So far, no clinical trials have been reported with partial subtype-selective GABA<sub>A</sub> agonists.
The lack of significant CNS effects does not seem to be related to low plasma concentrations. In our study, the plasma levels were comparable to those in rats receiving doses that produced anxiolytic-like effects in the punished drinking test and elevated plus-maze test [3,4]. Plasma levels were high compared to lorazepam, which is in keeping with the relatively low affinity of SL65.1498 for the GABA<sub>A</sub> receptor subtypes (Ki: 6.8-117 nM) compared to those of other GABA<sub>A</sub> receptor ligands [31]. Healthy humans showed small CNS-effects on some CNS-functions but not on others, at plasma concentrations of SL65.1498 that were anxiolytic but devoid of sedative effects in animal models [3,5]. This could be related to the selective pharmacological profile of SL65.1498. However, selectivity cannot be proven, since none of the three doses of SL65.1498 was equipotent to lorazepam for any effect that was measured. To date the compound has not been registered, and no results of clinical trials in anxiety or other conditions have been published. The putative wider therapeutic window that is suggested by preclinical experiments and supported by our results cannot therefore be confirmed at present.

The current study showed that SL65.1498 at doses of 2.5-25 mg is well tolerated and induces no impairments on memory, sedation and psychomotor and cognitive functions. It is unclear whether this is related to subtype selectivity or to relatively low doses.
Table 1  Pharmacodynamic differences in AUE 0-6hr relative to baseline for Saccadic Eye Movements, Smooth Pursuit Performance, Visual Analogue Scales and Body Sway. ANOVA results are shown as contrasts (95% CI) with p-value.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall treatment effect (p-value)</th>
<th>Placebo - 1.5 g 2.5 mg</th>
<th>Placebo - 1.5 g 7.5 mg</th>
<th>Placebo - 1.5 g 14mg 25 mg</th>
<th>Lorazepam 2 mg - 1.5 g 25 mg</th>
<th>Placebo - 1.5 g 25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccadic Peak Velocity (deg/sec)</td>
<td>0.0001</td>
<td>5.52 (4.41/6.66)</td>
<td>8.07 (1.86/7.99)</td>
<td>15.02 (5.00/24.94)</td>
<td>30.67 (20.73/40.60)</td>
<td>45.69 (35.76/55.62)</td>
</tr>
<tr>
<td>Smooth pursuit (%)</td>
<td>0.0001</td>
<td>0.62 (-2.96/4.19)</td>
<td>1.21 (-2.37/4.70)</td>
<td>5.27 (1.60/8.84)</td>
<td>-12.73 (-16.31/-9.15)</td>
<td>18.00 (14.42/21.57)</td>
</tr>
<tr>
<td>Alertness (ln mm)</td>
<td>0.0001</td>
<td>1.42 (-24.68/27.52)</td>
<td>3.63 (-22.47/20.73)</td>
<td>-13.01 (-3.91/13.09)</td>
<td>82.54 (56.44/108.63)</td>
<td>-95.54 (-121.64/-69.45)</td>
</tr>
<tr>
<td>Contendedness (ln mm)</td>
<td>0.0356</td>
<td>-3.95 (-12.83/-4.94)</td>
<td>1.78 (-7.11/10.66)</td>
<td>-2.15 (-1.05/-3.74)</td>
<td>9.53 (0.64/18.41)</td>
<td>-11.67 (-20.55/-2.79)</td>
</tr>
<tr>
<td>Calmness (ln mm)</td>
<td>0.4971</td>
<td>-1.19 (-6.84/4.64)</td>
<td>0.09 (-5.96/5.76)</td>
<td>1.20 (-4.45/6.83)</td>
<td>1.46 (-4.19/7.11)</td>
<td>-0.26 (-5.91/5.30)</td>
</tr>
<tr>
<td>Body Sway Eyes Closed (mm)</td>
<td>0.0001</td>
<td>6.0 (11.0/21.0)</td>
<td>6.0 (11.0/21.0)</td>
<td>2.0 (-14.0/21.0)</td>
<td>54.0 (-62.0/46.1)</td>
<td>-225.0 (-285/-165)</td>
</tr>
</tbody>
</table>
Table 2  Mean number of correct responses (SEM) for immediate word recall (three consecutive trials) and delayed word recall and recognition.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Immediate word recall</th>
<th>Delayed</th>
<th>Word Recall</th>
<th>Word Recognition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st trial</td>
<td>2nd trial</td>
<td>3rd trial</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Mean: 11.1 SEM: 0.7</td>
<td>Mean: 15.0 SEM: 0.9</td>
<td>Mean: 18.1 SEM: 1.1</td>
<td>Mean: 16.2 SEM: 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5165.1498 2.5 mg</td>
<td>9.2* SEM: 0.7</td>
<td>Mean: 15.2 SEM: 0.9</td>
<td>Mean: 17.9 SEM: 1.5</td>
<td>Mean: 15.2 SEM: 1.4</td>
</tr>
<tr>
<td>5165.1498 7.5 mg</td>
<td>10.3 SEM: 0.7</td>
<td>Mean: 15.0 SEM: 0.9</td>
<td>Mean: 17.4 SEM: 1.1</td>
<td>Mean: 15.2 SEM: 1.2</td>
</tr>
<tr>
<td>5165.1498 25 mg</td>
<td>10.0 SEM: 0.8</td>
<td>Mean: 14.5 SEM: 0.9</td>
<td>Mean: 16.2 SEM: 1.1</td>
<td>Mean: 14.8 SEM: 1.4</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>5.6 SEM: 0.6</td>
<td>Mean: 8.6 SEM: 0.9</td>
<td>Mean: 11.1 SEM: 0.9</td>
<td>Mean: 7.4 SEM: 1.0</td>
</tr>
</tbody>
</table>

Bold values show significant effects compared to placebo (p < 0.0001, * p < 0.05).

Table 3  Mean latency times for correct response (SEM) for auditory and visual reaction time tests and mean number of correct responses (SEM) for binary choice reaction time test.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Auditory reaction time test</th>
<th>Visual reaction time test</th>
<th>Binary Choice reaction time test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean latency for correct response (ms)</td>
<td>Mean latency for correct response (ms)</td>
<td>Mean number correct</td>
</tr>
<tr>
<td>Placebo</td>
<td>Mean: 250.40 SEM: 6.16</td>
<td>Mean: 271.45 SEM: 6.60</td>
<td>Mean: 58.4 SEM: 0.4</td>
</tr>
<tr>
<td>5165.1498 2.5 mg</td>
<td>259.20 SEM: 7.27</td>
<td>Mean: 275.75 SEM: 7.04</td>
<td>Mean: 58.2 SEM: 0.4</td>
</tr>
<tr>
<td>5165.1498 7.5 mg</td>
<td>253.20 SEM: 6.75</td>
<td>Mean: 280.60 SEM: 7.56</td>
<td>Mean: 58.2 SEM: 0.6</td>
</tr>
<tr>
<td>5165.1498 25 mg</td>
<td>259.60 SEM: 5.21</td>
<td>Mean: 290.45 SEM: 15.83</td>
<td>Mean: 58.4 SEM: 0.3</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>301.90 SEM: 13.49</td>
<td>Mean: 360.70 SEM: 31.38</td>
<td>Mean: 58.0 SEM: 0.7</td>
</tr>
</tbody>
</table>

Bold values show differences compared to placebo (p < 0.0001)
Figure 1  Average plasma drug concentration-time profiles (mean + SD)

![Graph showing plasma drug concentration-time profiles with SD error bars for different doses of a drug.]

Figure 2  Average graph of Saccadic Peak Velocity (deg/sec) with SD error bars for Placebo (up) and Lorazepam 2 mg (down). Open circle: 2.5 mg; open square: 7.5 mg; open triangle: 25 mg. Closed circle: Lorazepam 2 mg; closed square: Placebo.

![Graph showing saccadic peak velocity over time for different doses of a drug.]

Pharmacological differences of gabaergic compounds: a pharmacodynamic characterization.
Figure 3  Average graph of Smooth Pursuit (%) with SD error bars for Placebo (up) and Lorazepam 2 mg (down). Open circle: SL 2.5 mg open square: SL65.1498 7.5 mg open triangle: SL65.1498 25 mg closed circle: Lorazepam 2 mg closed square: Placebo.

Figure 4  Average graph of VAS alertness (mm) with SD error bars for Lorazepam 2 mg (up) and Placebo (down). Open circle: SL 2.5 mg open square: SL65.1498 7.5 mg open triangle: SL65.1498 25 mg closed circle: Lorazepam 2 mg closed square: Placebo.
Figure 5  Average graph of Body Sway (mm) with SD error bars for Lorazepam 2 mg (up) and Placebo (down). Open circle: SL 2.5 mg open square: SL65.1498 7.5 mg open triangle: SL65.1498 25 mg closed circle: Lorazepam 2 mg closed square: Placebo.
REFERENCES


