CHAPTER 3

Pharmacodynamic and pharmacokinetic effects of MK-0343, a GABAA α2,3 subtype selective agonist, compared to lorazepam and placebo in healthy male volunteers


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ABSTRACT

The use of nonselective GABA enhancers, such as benzodiazepines in the treatment of anxiety disorders is still widespread but hampered by unfavourable side-effects. Some of these may be associated with binding properties to certain subtypes of the GABA<sub>A</sub> receptor that are unnecessary for therapeutic effects. MK-0343 was designed to be a less sedating anxiolytic, based on reduced efficacy at the α<sub>1</sub> subtype and significant efficacy at α<sub>2</sub> and α<sub>3</sub> subtypes of the GABA<sub>A</sub> receptor.

This study was a double-blind, 4-way cross-over (n=12) study to investigate the effects of MK-0343 (0.25 and 0.75 mg) in comparison to placebo and an anxiolytic dose (2mg) of the non-selective agonist lorazepam. Effects were measured by eye movements, body sway, Visual Analogue Scales and memory tests.

Lorazepam impaired Saccadic Peak Velocity (SPV), VAS alertness scores, postural stability and memory and increased saccadic latency and inaccuracy. MK-0343 0.75 mg was equipotent with lorazepam as indicated by SPV (-42.4 deg/sec), saccadic latency (0.02 sec) and VAS alertness scores (1.50 ln mm), while effects on memory and postural stability were smaller. MK-0343 0.25mg only affected postural stability to a similar extent as MK-0343 0.75mg.

The effect profile of MK-0343 0.75 mg is different from the full agonist lorazepam, which could reflect the selective actions of this compound. Although less effect on VAS alertness was expected, diminished effects on memory and postural stability were present. Clinical studies in anxiety patients should show whether this dose of MK-0343 is therapeutically effective with a different side-effect profile.
INTRODUCTION

Benzodiazepines are effective and widely used for the treatment of panic disorder and generalised anxiety disorder. Despite the effectiveness of these drugs, the clinical usefulness is limited due to side effects like amnesia, ataxia, sedation and impaired concentration and memory [1,2]. Tolerance and abuse are additional problems after long-term use [3]. This side-effect profile is caused by the non-selective properties of benzodiazepines for the different α-subtypes of the GABA<sub>A</sub> receptor [4]. The non-selective full agonist benzodiazepines led to the development of non-selective partial agonists with a lower maximum effect for some of the adverse properties. Although the preclinical profile improved, a translation to non-sedating anxiolytics failed [5-7]. Subsequently, rodent studies revealed the involvement of the different GABA<sub>A</sub> subtypes [4,8-12]. Knock-in and knock-out mice experiments clarified the association between the GABA<sub>A</sub> subtypes and their pharmacological response. This knowledge has stimulated the search for ligands for different GABA<sub>A</sub>-receptor subtypes, with a purported higher therapeutic selectivity and an improved side effect profile.

Pre-clinical studies indicated that the α<sub>2,3</sub> subunit of the GABA<sub>A</sub> receptor is responsible for anxiolysis and muscle relaxation [11,13-15], while the α<sub>1</sub> subunit is involved in sedation [8,10,12,16]. MK-0343 is a compound with a low efficacy at the α<sub>1</sub> and α<sub>5</sub> subunit (both 18% relative to chlordiazepoxide) and a high efficacy at the α<sub>2,3</sub> subunit of the GABA<sub>A</sub> receptor (23 and 45% respectively), as assessed by wholecell patch clamp recordings with human recombinant GABA<sub>A</sub> receptors (MSD, data on file). Based on its functional selectivity and the results in several animal models it was thought to have anxiolytic efficacy while being less sedating compared to benzodiazepines.

The maximum tolerated dose (MTD) of MK-0343 in healthy volunteers was 1.0 mg, as moderate and severe drowsiness was reported by two of the six subjects after a single dose of 2 mg (MSD, data on file). The doses chosen for this current study of 0.25 and 0.75 mg, represented 1/4 and 3/4 of the MTD. A full pharmacodynamic evaluation of the higher dose of MK-0343 (0.75 mg) would provide an assessment of the greatest sedative, cognitive, and motor effects expected with this drug in subsequent clinical development. The lower dose of MK-0343 (~0.25 mg MTD) was also tested in order to establish the pharmacodynamic effects expected at a dose that, while substantially lower than the high dose, might still demonstrate anxiolytic efficacy. Pharmacodynamic (PD) measurements included eye movements, body sway measurements, Visual Analogue Scales and memory testing, which have all been shown to be highly sensitive to the effects of non-selective benzodiazepines [5,17-19]. MK-0343 was compared
to lorazepam 2 mg, which is known to be therapeutically relevant, mildly sedative [20,21] and known to affect these PD measurements [19]. The more selective character of MK-0343 was expected to lead to diminished subjective sedation, reduced postural instability and less memory impairment, compared to a benzodiazepine. In contrast, MK-0343 was expected to cause SPV reduction. This parameter has been shown to be associated with the anxiolytic effects of benzodiazepines [22], and a previous study with the selective GABA \(_{\alpha}2,3\) partial agonist TPA023 showed effects only on SPV. Similar results could therefore be expected in the current study.

**METHODS**

**Design**

This study was a placebo controlled, randomised, double-blind, double-dummy, four-way, cross-over, single-centre study in twelve healthy male volunteers, with at least a five-day washout period.

**Subjects**

Twelve healthy non-smoking volunteers were recruited from the database of the Centre for Human drug Research (CHDR) and gave written informed consent before medical screening. Subjects were asked not to drink alcohol 48 hours prior to the study, abstain from caffeine-containing products 8 hours prior to the study and from grapefruit (juice) and St John’s Wort at least 2 weeks prior to study start until completion of the study. The study was approved by the Medical Ethics Review Board of Leiden University medical Centre, and performed according to their standards.

**Treatments**

Each subject received a single oral dose MK-0343 0.25mg, MK-0343 0.75mg, lorazepam 2mg or placebo, administered with 250 ml of water in a fasted state at approximately 9 to 10 AM on each treatment day. To maintain blinding, subjects always received 3 tablets of MK-0343 or matching placebo plus 2 capsules of lorazepam or matching placebo. The treatment sequences were determined using 4x4 Latin Squares, balanced for 1st order carry-over.
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.

Drug analyses

Blood samples (5ml) were drawn on each occasion day within 30 minutes predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 24 hours postdose, and were processed to obtain plasma for assay of MK-0343 concentrations. Lorazepam concentrations were not determined. Plasma was separated from heparinized blood samples by centrifugation (2000 gs, 10 min, 4°C) to 3.6 cc Nunc cryotubes and stored at -20°C within 30 minutes after sampling. MK-0343 analysis was accomplished by solid phase extraction of the analyte and an internal standard from plasma using a 96-well plate format followed by reversed phase HPLC and ms/ms detection.

Pharmacodynamics

Pharmacodynamic measurements were performed predose (within 30 minutes prior to dosing) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 10 hours postdose. Subjects underwent pharmacodynamic tests individually in a quiet room with ambient illumination. Each session consisted of the following sequence of tests: saccadic eye movements; body sway eyes open/closed; vas. Cognitive function tests were performed in the 1-3 hours-postdose period between the other measurements.

Saccadic Eye Movements

Saccadic eye movements were recorded using a 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-00-5, Olstykke, Denmark) [23]. Average values of latency (= reaction time), peak saccadic velocity and inaccuracy (difference between stimulus angle and corresponding saccade in %) were calculated for all artifact-free saccades. Saccadic peak velocity has been validated as the most
sensitive measure for the sedative effects of benzodiazepines [17,18]. Saccadic peak velocity has also been shown to be closely related to the anxiolytic properties of benzodiazepines [22].

Visual analogue scale

Visual analogue scales as originally described by Norris [24] were previously used to quantify subjective effects of benzodiazepines [17]. From the set of sixteen scales three composite factors were derived as described by Bond and Lader [25], corresponding to alertness, mood 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 [26], 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 open and 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 [5].

Cognitive function tests

Memory testing was performed between one to three hours postdose, using the validated FePsy program (The Iron Psyche), an automated system containing a battery of computerised tests for cognitive (neuropsychological) functions [27,28]. Word and picture recognition and recall tests were performed after presentation of words and pictures serially and simultaneously. Reaction time and number of correct and incorrect answers were assessed. The Corsi block tapping test, constructed according to the principles of the original Corsi block tapping task [29], assessed the nonverbal memory span. Memory tests have been shown to be affected by benzodiazepines [19,30].

ANALYSIS

Pharmacokinetics

Pharmacokinetics of MK-0343 were determined using an one-compartment model with first order absorption and a lag-time. Parameters determined were absorption half-life, absorption lag-
time, apparent clearance (clearance divided by bioavailability) and elimination half-life. A constant coefficient of variation error model was used. Estimation was performed using NONMEM software (NONMEM Version V, GloboMax LLC, Hanover, MD, USA) providing NONMEM population estimates using the first-order conditional estimation method with interaction.

Statistics

Treatment response was characterised for continuously measured variables by calculating the area under the effect curve (AUEC) relative to baseline over 6 hours. The two pre-values were averaged and set at time = 0 hr. Change from average pre-value (delta) was calculated. The AUECs 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 changes from pre-value. All variables were analysed untransformed except for body sway, because only body sway clearly indicated an increase in variability in response with an increase in average response. 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 (using a p-value cut-off of 5%), the analysis was rerun without the carry-over factor. The four treatments were compared within the ANOVA model using the following contrasts: placebo - MK-0343 0.25mg, placebo - MK-0343 0.75mg, lorazepam 2mg - MK-0343 0.75mg and placebo - lorazepam 2mg. Overall p-value for the treatment effect was reported along with the specified contrasts with 95% confidence intervals and p-values.

All calculations were performed using SAS for Windows V8.2 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Subjects

Twelve male subjects underwent medical screening after giving written informed consent and completed the study. Subjects had a mean age of 25 years (range 18-30), weight of 78 kg (range 55-98 kg) and height of 183 cm (range 178-192 cm).
Clinical observations

No serious adverse reactions occurred following any treatment. The most frequently reported adverse event (AE) was fatigue after administration of lorazepam (seven subjects), and the high and low doses of MK-0343 (five and three subjects, respectively). Other reported adverse events were sleepiness after MK-0343 0.25 mg and 0.75 mg administration (four subjects in each group) and lorazepam (two subjects), drowsiness after MK-0343 0.25 mg and 0.75 mg administration (four and three subjects, respectively) and lorazepam (six subjects) and headache after MK-0343 0.25 mg and 0.75 mg (two subjects in each group) and lorazepam (three subjects). In the placebo group fatigue and sleepiness were each reported by one subject. All AEs were of mild intensity, except for three severe sedative-related AEs in the lorazepam group. The AEs in the lorazepam group were, on average, of longer duration than those in the MK-0343 groups.

Pharmacokinetics

The average plasma concentration-time curves for both doses of MK-0343 are shown in figure 1. Both doses of MK-0343 showed maximum concentrations after approximately 1 hour. The $C_{\text{MAX}}$ (mean (SD)) was 9.23 (1.58) ng/mL for the higher dose and 3.25 (0.57) for the lower. NONMEM population PK parameters obtained (mean (coefficient of inter-individual variability)) were an absorption half-life of 3.09 min (82%), an absorption lag time of 24.8 min (0.4%), a Clearance/F of 0.391 L/min (22%), an elimination half-life of 126 min (15%), and a residual variability of 7.0%.

Pharmacodynamics

Saccadic Eye Movements

Saccadic Peak Velocity (SPV) was decreased by MK-0343 0.75 mg and lorazepam 2 mg (42.4 deg/sec and 51.6 deg/sec respectively) (table 1, figure 2). These treatments also increased saccadic latency, while only lorazepam affected saccadic inaccuracy (table 1).

Visual Analogue Scales

Lorazepam caused the largest effects on VAS alertness (figure 3), while the effects of the higher dose of MK-0343 were somewhat smaller but also different from placebo (table 1). No changes occurred after the low dose of MK-0343 compared to placebo (table 1). None of the treatments did affect the VAS contentedness and calmness scale.
Body Sway
Both doses of MK-0343 increased body sway (eyes closed) to a similar extent (0.26 logmm; 95%CI: 0.08/0.44 and 0.22 95%CI: 0.05/0.40) (figure 4). The effects differed from placebo and from the larger effects of lorazepam (table 1). Body sway measurements with open eyes were only affected by lorazepam intake (-0.51 logmm; 95%CI: -0.673/-0.348).

Cognitive Function Tests and Corsi Block Tapping Task
No treatment effects were observed on the Corsi block tapping test for both doses of MK-0343 (0.75 mg: 0.33 95%CI: -0.50 / 1.17) or lorazepam (0.42 95%CI: -0.42 / 1.25). For the recognition tests, only lorazepam decreased the number of correct words in the test with simultaneous words compared to placebo and MK-0343 0.75 mg. Lorazepam increased the reaction times of the correct answers in all tests compared to placebo and MK-0343 0.75 mg, while MK-0343 0.75 mg itself only increased the reaction time in one test compared to placebo (Figure 5).

The lower dose of MK-0343 did not show any effect on the cognitive function test, nor the Corsi block tapping task.

DISCUSSION
This study was performed to determine the CNS effects of two doses of a new subtype selective GABA_A agonist, MK-0343, and to compare them to those of placebo and the full agonist lorazepam.
Pre-clinical studies showed that MK-0343 acts as a partial agonist at α2,3 subtypes, with less efficacy at α1 and α5 subtypes (MSD, data on file). The selective efficacy profile of this compound seems to be reflected in the clinical effect profile in this study. As expected from previous studies with benzodiazepines [5,17-19], lorazepam impaired saccadic eye movements, VAS alertness scores, memory and postural stability. The higher dose of MK-0343 caused similar reductions in saccadic peak velocity (SPV) and VAS alertness scores compared to lorazepam, showing rough equipotency for these CNS-effects. In contrast, effects on postural stability and memory were present to a significantly lesser degree with the subtype specific agent than with the full benzodiazepine agonist. Although the therapeutic equipotency is not yet known due to lack of studies with MK-0343 in anxiety patients, both doses of MK-0343 are anxiolytic in pre-clinical studies. The current study suggests that MK-0343 will show less memory impairment and postural instability than lorazepam in patient studies.
Pre-clinical studies indicated that the $\alpha_{2,3}$ subunit of the GABA$_A$ receptor is responsible for anxiolysis and muscle relaxation [11,13-15], while the $\alpha_1$ subunit is involved in sedation [8,10,12,16]. These findings have stimulated the search for ligands for different GABA$_A$ receptor subtypes, with a higher therapeutic selectivity. Alpha-1 selective agents were developed for the indication of insomnia, while $\alpha_{2,3}$ selective compounds were developed as anxiolytics.

Pre-clinical studies showed that MK-0343 was anxiolytic in different rodent models and one primate model, similar to the effects of diazepam (MSD, data on file). Sedation models like the mouse rotarod test, the rat sensitivity test and an equivalent monkey test showed a clear separation between the doses required to produce sedation and anxiolysis. However, it is still unclear if the preclinical mechanisms seen in rodents and to a lesser extent in primates can be translated to humans. So far, the non-selective partial agonists bretazenil and abecarnil have failed as they did not have sufficient separation between anxiolytic and sedative effects [31]. In this respect, a partial agonist seems to behave much like a low dose of a full agonist, with a built in limit to its adverse as well as therapeutic efficacy. In theory, subtype selective compounds should not have this disadvantage, although it has proven difficult to translate this into practice. For a few compounds, like L-888417 [32], compound 4 [33] and nsx, only pre-clinical results have been published yet. For TPA023, pre-clinical and human, although not patient, data are available [19,34,35]. Development of other compounds has been stopped due a lack of anxiolytic efficacy [36,37] despite very promising pre-clinical data. Only ocinaplon [38] and ELB139, a GABA$_A$ $\alpha_3$ subtype-selective agonist [39], seem to be most advanced in their clinical development [36]. Unexpectedly, ocinaplon seems anxiolytic and non-sedating in patients despite a relatively $\alpha_1$ subtype selective efficacy profile [38]. This does not seem consistent with the other pre-clinical data and hypotheses that anxiolysis is mediated by GABA$_A$ $\alpha_2$ and $\alpha_3$, and sedation by $\alpha_1$ receptor subtypes [11,13,14]. These inconsistencies could reflect differences in preclinical predictivity of GABA$_A$ subtype-selectivity for the situation in humans. This may explain that such a small number of subtype-selective compounds have so far been shown to be therapeutically relevant. Comparison of adverse and clinical effect profiles, for different subtype-selective and non-selective GABA$_A$ agonists will improve the predictability of preclinical experiments with these compounds.

The differences in effects in the current study compared to lorazepam are very likely to reflect the selective efficacy profile of MK-0343, although they do not necessarily correspond with preclinical predictions. VAS alertness was decreased for both the higher dose of MK-0343 and lorazepam, which suggests that the sedative effects
for both lorazepam 2mg and MK-0343 0.75 mg are similar. This was not expected, based on the low efficacy at the α1 subtype of the compound. The lower dose of MK-0343 did not show significant effects on VAS alertness scores. But for this dose no significant SPV-reductions were present, and this dose was not equipotent to lorazepam for any effect that was measured.

The different results of this study are in some ways comparable to those of a previous study of our research group, in which another α2,3 selective partial GABA_A agonist, TPA023, was studied [19]. However, in that study no effects on VAS alertness, postural stability and memory were present, while similar SPV-reductions were seen compared to lorazepam. The difference in efficacy profiles between the two compounds could be responsible for the differences in pharmacodynamic effects seen in human. Although both compounds share a selectivity for the α2,3 subtype, TPA023 is an antagonist at the α1 and α5 subtype while MK-0343 has shown low but at least some efficacy at these subtypes (relative efficacy 18% for both). It could be that the low efficacy at the α1 subtype is already enough to induce sedative effects, even similar to those of the full-agonist lorazepam, as seen in this study.

This low efficacy of MK-0343 at the α1 subtype could also be responsible for the effects on postural stability, although they were much smaller compared to the effects of lorazepam. This association is supported by the fact that zolpidem, selective for the α1 subtype, also increases body sway even more than diazepam [40] and that benzodiazepine induced ataxia was blocked in monkeys by an α1 GABA_A receptor selective antagonist [41]. This may represent a significant therapeutic advantage of MK-0343, since several studies have shown that benzodiazepines increase body sway [42,43] and cause falls due to postural instability in elderly [44].

MK-0343 did not show any effects on memory. Lorazepam affected all memory reaction times, but only one of the four memory tests (serial word recognition). Consequently, the contrast with MK-0343 was small, and it cannot be fully excluded that the observed lack of memory effects of MK-0343 is due to an insensitivity of the memory tests in this study. However, a previous study with TPA023 showed no memory effects of the partial subtype selective GABA_A agonist, as opposed to significant impairment on all tests with lorazepam [19]. This suggests that subtype-selective partial GABA_A agonists with low α5-efficacy are memory sparing in humans.

The current study has shown that the subtype-selective GABA_A agonist MK-0343 has a different effect profile compared to the benzodiazepine lorazepam. These differences may reflect the subtype-selectivity, although more subjective sedation was observed with the higher dose than would be expected from preclinical predictions.
Although this could translate into an improved safety profile, the clinical meaning of these differences is not yet fully known, because the anxiolytic dose of MK-0343 has not been established. Future studies in patients with anxiety disorders should reveal if anxiety can be suppressed using a dose of MK-0343 with relative few side effects.
## Table 1 Differences in pharmacodynamic measurements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall treatment effect (p-value)</th>
<th>Placebo - MK-0343 0.25mg</th>
<th>Placebo - MK-0343 0.75mg</th>
<th>Lorazepam 2mg - MK-0343 0.75mg</th>
<th>Placebo - Lorazepam 2mg</th>
</tr>
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<tbody>
<tr>
<td>Saccadic Peak Velocity (deg/sec)</td>
<td>&lt;.0001</td>
<td>42.37</td>
<td>26.24</td>
<td>-1.26</td>
<td>51.63</td>
</tr>
<tr>
<td></td>
<td>p = 0.155</td>
<td>F = 2.13</td>
<td>F = 0.00</td>
<td>p = 0.251</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(-4.63 / 27.71)</td>
<td>(-25.43 / 6.91)</td>
<td>(-25.43 / 6.91)</td>
<td>(35.46 / 67.80)</td>
<td>F = 42.51</td>
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<tr>
<td>Saccadic Latency (sec)</td>
<td>&lt;.0001</td>
<td>-0.015</td>
<td>-0.025</td>
<td>0.014</td>
<td>-0.029</td>
</tr>
<tr>
<td></td>
<td>p = 0.003</td>
<td>F = 0.00</td>
<td>F = 0.00</td>
<td>p = 0.005</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(-0.009 / 0.010)</td>
<td>(-0.025 / -0.006)</td>
<td>(-0.025 / -0.006)</td>
<td>(-0.039 / -0.020)</td>
<td>F = 40.32</td>
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<tr>
<td>Saccadic Inaccuracy (%)</td>
<td>0.058</td>
<td>-1.54</td>
<td>-3.66</td>
<td>1.45</td>
<td>-2.99</td>
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<tr>
<td></td>
<td>p = 0.335</td>
<td>F = 0.06</td>
<td>F = 0.06</td>
<td>p = 0.173</td>
<td>p &lt; 0.001</td>
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<tr>
<td></td>
<td>(-1.14 / 1.10)</td>
<td>(-3.66 / 0.97)</td>
<td>(-3.66 / 0.97)</td>
<td>(-5.11 / -0.87)</td>
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<tr>
<td>vas Alertness (ln mm)</td>
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<td>-1.50</td>
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<td>0.31</td>
<td>-1.81</td>
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<tr>
<td></td>
<td>p = 0.004</td>
<td>F = 0.75</td>
<td>F = 0.75</td>
<td>p = 0.325</td>
<td>p &lt; 0.001</td>
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<tr>
<td></td>
<td>(-1.86 / -0.10)</td>
<td>(-2.40 / -0.52)</td>
<td>(-2.40 / -0.52)</td>
<td>(-2.80 / -0.83)</td>
<td>F = 14.14</td>
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<tr>
<td>vas Contentedness (ln mm)</td>
<td>0.004</td>
<td>-0.30</td>
<td>-0.18</td>
<td>0.08</td>
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<tr>
<td></td>
<td>p = 0.208</td>
<td>F = 1.66</td>
<td>F = 0.56</td>
<td>p = 0.733</td>
<td>p = 0.354</td>
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<tr>
<td></td>
<td>(-0.31 / 0.93)</td>
<td>(-0.18 / 0.70)</td>
<td>(-0.40 / 0.56)</td>
<td>F = 0.12</td>
<td>(-0.26 / 0.70)</td>
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<tr>
<td>vas Calmness (ln mm)</td>
<td>0.211</td>
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<td>-0.15</td>
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<td>(-0.16 / 0.65)</td>
<td>(-0.30 / 0.51)</td>
<td>(-0.30 / 0.51)</td>
<td>(-0.56 / 0.25)</td>
<td>(-0.14 / 0.67)</td>
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<td>Log Body Sway Eyes Closed (log mm)</td>
<td>0.001</td>
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<td>-0.224</td>
<td>0.24</td>
<td>-0.471</td>
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<tr>
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<td>p = 0.016</td>
<td>F = 6.55</td>
<td>F = 6.55</td>
<td>p = 0.008</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(-0.401 / -0.046)</td>
<td>(-0.401 / -0.046)</td>
<td>(-0.401 / -0.302)</td>
<td>(-0.650 / -0.292)</td>
<td>F = 28.84</td>
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<td>Log Body Sway Eyes Open (log mm)</td>
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<td>-0.152</td>
<td>0.358</td>
<td>-0.511</td>
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<td>p = 0.065</td>
<td>F = 1.69</td>
<td>F = 1.69</td>
<td>p &lt; 0.001</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>(-0.315 / 0.10)</td>
<td>(-0.315 / 0.10)</td>
<td>(-0.315 / 0.521)</td>
<td>(-0.673 / -0.348)</td>
<td>F = 41.22</td>
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</table>

Pharmacodynamic measurements in AUC 0-6hr relative to baseline for Saccadic Eye Movements, Visual Analogue Scales and Body Sway ANOVA results are shown as contrasts (95% CI) p-value and F-value (1, 30 df).
Figure 1  Average drug concentration profiles (mean + SD) of MK-0343 0.25mg (squares), MK-0343 0.75mg (circles) after oral administration.

![Graph of drug concentration profiles](image1)

Figure 2  Average time profile (mean + SD) of Saccadic Peak Velocity (change from baseline) after oral administration of placebo (closed circles), MK-0343 0.25mg (squares), MK-0343 0.75mg (open circles) and lorazepam 2mg (triangles).

![Graph of saccadic peak velocity](image2)
Figure 3  Average time profile (mean + SD) of VAS Alertness (change from baseline) after oral administration of placebo (closed circles), MK-0343 0.25mg (squares), MK-0343 0.75mg (open circles) and lorazepam 2mg (triangles).

Figure 4  Average time profile (mean + SD) of LOG Body Sway Eyes Closed (change from baseline) after oral administration of placebo (closed circles), MK-0343 0.25mg (squares), MK-0343 0.75mg (open circles) and lorazepam 2mg (triangles).
Figure 5  Effects on cognitive function tests (mean + SD).

RFSE = Recognition Figures Serial; RFSI = Recognition Figures Simultaneous; RWSE = Recognition Words Serial; RWSI = Recognition Words Simultaneous.
†: p<0.05 compared to placebo; ‡: p<0.05 compared to placebo and MK-0343 0.75mg.
agents in early phase drug development


