A question based approach to drug development

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CHAPTER 11

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SUBMITTED

Pharmacodynamic and pharmacokinetic effects of MRLA023, a $GABA_A$ $\alpha_{2,3}$ subtype selective agonist, compared to lorazepam and placebo in healthy volunteers

Abstract

AIM This study investigated the effects of two doses (0.5 mg and 1.5 mg) of MRLA023, which is a $GABA_A$ $\alpha_{2,3}$ subtype selective partial agonist. This compound MRLA023 is expected to result in comparable anxiolytic efficacy as clinically used benzodiazepines with an improved tolerability profile. It is hypothesised to be less sedating because it lacks efficacy at the α_1 subtype, the subtype believed to mediate the sedative effects of benzodiazepines.

MATERIAL AND METHODS Twelve healthy male volunteers participated in this placebo controlled, double-blind, double-dummy, four-way, cross-over study. As a positive control, the non-selective benzodiazepine lorazepam (2mg) was used in a therapeutic anxiolytic dose. The Central Nervous System (CNS) effects of the two doses of MRLA023 and lorazepam were compared with placebo. Saccadic Eye Movements (SEM) and Visual Analogue Scales (VAS) were used to assess the sedative properties of MRLA023. The psychomotor and cognitive effects were assessed using body sway and a standardised battery of neurophysiological memory tests.

RESULTS Lorazepam caused sedation (maximum SEM reduction of 89 deg/sec and a VAS alertness score maximum effect of 4.5 mm) and impairment of memory and body stability (three of the four memory tests studied showed significant memory impairment and body sway with eyes closed was increased by 28%). MRLA023 had significant dose dependent effects on SEM (85 deg/sec maximum reduction at the higher dose, approximating that of lorazepam) but not on VAS score of alertness. No changes were observed in saccadic latency and saccadic inaccuracy for either doses of MRLA023, in contrast to significant increases with lorazepam. Contrary to lorazepam, MRLA023 caused no detectable memory impairment or postural imbalance.

CONCLUSION These results show that the effect profile of MRLA023 differs from that of lorazepam, at doses that were equipotent with regard to SEM -effects. Therapeutic equipotency cannot be proven at this stage, because the clinical effects of MRLA023 have not yet been determined. The differentiation between pharmacodynamic effects for the selective $GABA_A$ agonist MRLA023 may be related to selectivity for different $GABA_A$ receptor subtypes. Further studies will show whether this pharmacological selectivity is associated with an improved side effect profile.

Introduction

Generalised anxiety disorder (GAD) is a severe, chronic, and distressing illness that often requires long-term management. The lifetime prevalence is approximately 4 to 6 percent in the general population and is more common in women than in men. Benzodiazepines are the most frequently prescribed pharmacological treatment for GAD. Benzodiazepines possess several advantages over other anxiolytics, including rapid action, ease of use and a wide margin of safety. Although benzodiazepines are relatively safe drugs and are widely used in the treatment of anxiety, they may produce untoward side effects such as sedation, memory impairment and muscle relaxation.

ref. 1

MRLA023 is a $GABA_A$ $\alpha_{2,3}$ subtype selective partial agonist, which is expected to result in comparable anxiolytic efficacy as clinically used benzodiazepines with an improved tolerability profile based upon pre-clinical animal models. In particular, MRLA023 has the potential to be an effective, non-sedating anxiolytic. It is believed to be non-sedating because it lacks efficacy at the α_1-subtype, the subtype believed to mediate the sedative effects of benzodiazepines.

ref. 2-6

Based on tolerability findings in healthy volunteers, two doses of MRLA023 were selected for this study: 0.5 mg and 1.5 mg. The highest dose was chosen to evaluate the sedative, cognitive, and motor effects that could be expected with doses at the upper end of the anticipated dose range to be evaluated in further studies. The lower dose of MRLA023 was tested in order to establish the pharmacodynamic effects expected at a dose that might still demonstrate anxiolytic efficacy. For lorazepam, a dose of 2 mg was selected, which is known to be both therapeutically relevant and sedating.

ref. 7-8

The current study was designed to compare the central nervous system (CNS) effects of two dose levels of MRLA023 with those of placebo and 2 mg lorazepam in healthy male subjects. Saccadic eye movements and visual analogue scales were used to assess the sedative properties. According to a recent literature review of non-selective benzodiazepine anxiolytics, effects on saccadic eye movements are also closely correlated with therapeutic effects. In addition, the psychomotor and cognitive effects of MRLA023 were compared with those of 2 mg lorazepam and placebo, using body sway and a standardised psychometric battery. Finally, the plasma levels of MRLA023 were correlated with statistically significant pharmacodynamic effects.

ref. 9

Methods

Design

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

Subjects

Twelve healthy non-smoking volunteers were recruited from the CHDR database. All volunteers received a full medical examination and gave written informed consent before entry to the study. 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, grapefruit juice and St. John's Wort for at least 2 weeks prior to the study until the completion of the study. The study was approved by the Medical Ethics Review Board of Leiden University Medical Center, and performed according to the principles of the Helsinki Declaration and GCP.

Treatments

Subjects received each single oral dose MRLA023 0.5mg, MRLA023 1.5mg, lorazepam 2 mg or placebo administered with 250 ml of water in a fasting state at approximately 8 to 9 AM on day 1 of each study period. Subjects always received 3 tablets of MRLA023 or matching placebo and 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), 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 5 minutes.

Pharmacokinetics

Blood samples were drawn on day 1 of each occasion day predose (within 30 minutes prior to dosing) 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 MRLA023 and lorazepam concentrations. All blood samples were protected from exposure to direct light throughout the sample handling procedures. Blood samples (5 ml) drawn from an intravenous catheter were collected into sodium heparinised tubes. Blood samples were inverted 6 times and immediately centrifuged in a refrigerated centrifuge at 2000 gs for 10 minutes at 4°C. Plasma was transferred to a 4.5 cc Nunc cryotube and stored at −20°C within 30 minutes. Plasma samples collected following each MRLA023 dose were assayed for MRLA023. 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. Plasma samples collected following the lorazepam dose were assayed for lorazepam. Lorazepam and its stable-isotoped labelled internal standard were extracted from basified plasma into methyl-t-butyl ether with an automated procedure using a Tomtec Quadra 96 Model 320. Extracts were evaporated under nitrogen, reconstituted and analyzed by LC/MS/MS using positive ion Turbo Ionspray with multiple reaction monitoring.

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. Pharmacodynamic tests were perfomed 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: saccadic eye movements; body sway eyes open; body sway eyes 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 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). 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.

ref. 10

ref. 11-13

VISUAL ANALOGUE SCALE Visual analogue scales as originally described by Norris were previously used to quantify subjective effects of benzodiazepines. From the set of sixteen scales three composite factors were derived as described by Bond and Lader, corresponding to alertness, mood and calmness. These factors were used to quantify subjective drug effects.

ref. 14 ref. 13 ref. 15

BODY SWAY Body sway was measured with an apparatus similar to the Wright ataxiameter, 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.

ref. 16

COGNITIVE FUNCTION TESTS The neurophysiological memory tests were performed using FePsy (The Iron Psyche), an automated system containing a battery of computerised tests for cognitive (neuropsychological) functions. The recognition and recall test and the Corsi block tapping task were included in this study. The Corsi block tapping test was constructed according the principles of the original Corsi block tapping task. This task assessed the nonverbal memory span.

ref. 17 ref. 18

Analysis

PHARMACOKINETICS The pharmacokinetics of MRLA023 was investigated using non-linear mixed effect modeling as implemented in NONMEM version V software (NONMEM Project Group, University of California, San Francisco, CA), applying the first order conditional estimation (FOCE) method with the 'interaction' option. A series of PK models was attempted and compared using the likelihood ratio test. Ultimately, a two-compartment model with first-order absorption and a lag-time was used to describe the pharmacokinetics of MRLA023. Intra-individual error was modelled using a constant coefficient of variation error model. No pharmacokinetic parameters were calculated for lorazepam.

ref. 19

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS The observed pharmacodynamic effects were plotted against the predicted MRLA023 concentrations for each individual. Because the average placebo profile for saccadic peak velocity was not flat, the average placebo profile was subtracted from all saccadic peak velocity data at corresponding protocol time points and the result was subjected to PK/PD analysis. PK/PD modelling

was performed using non-linear mixed effect modelling as implemented in NONMEM. Empirical Bayes pharmacokinetics estimates were generated and used to describe the concentration profile for investigation of the PK/PD relationship between MRLA023 and saccadic peak velocity. A linear concentration-effect model was estimated without an effect compartment. Individual graphs indicated that no improvement could be obtained using either a more complex concentration-effect model or an effect compartment and further analysis was not attempted.

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 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 change 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, the analysis was rerun without the carry-over factor. The four treatments were compared within the ANOVA model using the following contrasts: placebo - MRLA023 0.5mg, placebo - MRLA023 1.5mg, lorazepam 2mg - MRLA023 1.5mg 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 V8.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Subjects

Twelve subjects, judged to be in good health on the basis of medical history, physical examination and routine laboratory data, participated in the study after giving written informed consent. Two subjects dropped out; one was repeatedly unable to swallow the capsules and another withdrew after the

second occasion for personal reasons. These two subjects were replaced by two other healthy male subjects, using the same randomisation sequence. Twelve subjects completed study. Subjects were on average 25 years of age (range 20-29), average weight of 82.3 kg (range 74.6-87.7 kg) and average height of 184.1 cm (range 177.6-191.9 cm).

Clinical observations

No serious adverse reactions occurred following any of the treatments. The most frequently reported adverse event was sedation by eight, five, zero and two subjects after administration of lorazepam, the high and low doses of MRLA023 and placebo, respectively. Other reported adverse events were drowsiness after MRLA023 0.5mg administration (three subjects), dizziness after MRLA023 1.5mg administration (four subjects), sleepiness and headache after lorazepam 2mg administration (seven and three subjects, respectively) and fatigue and headache after placebo administration (six and five subjects, respectively). ECG, blood pressure and heart rate measurements demonstrated no clinically significant effects for both doses of MRLA023, lorazepam and placebo.

Pharmacokinetics

The average plasma concentration-time curves for both doses of MRLA023 and lorazepam are shown in figure 1. Both doses of MRLA023 and lorazepam showed maximum concentrations after approximately 2 hours. The average pharmacokinetic parameters (with interindividual variation coefficients (CV) of MRLA023 were: clearance/bioavailability of 246 mL min^{-1} (CV 29%), initial half-life of 142 min (CV 6%), terminal half-life of 437 min (CV 0%, fixed), central volume of distribution/bioavailability of 71.1 L (CV 20%), absorption half-life of 33.6 min (CV 39%) and a lag-time of 27.4 min (CV 19%).

Pharmacodynamics

SACCADIC EYE MOVEMENTS Saccadic peak velocity (SPV), which was used to assess sedative properties, demonstrated significant effects with lorazepam and both doses of MRLA023 (figure 2 and table 1). There was a dose-dependent increase of SPV with MRLA023 0.5 and 1.5 mg ($AUEC_{0\text{-}6hr}$ decrease of 22 deg/sec and 45 deg/sec). No changes were observed in

saccadic latency and saccadic inaccuracy for either doses of MRLA023, in contrast to the significant increases with lorazepam. The high dose of MRLA023 and lorazepam caused similar average maximum effects on SPV relative to baseline. However, the effects of lorazepam lasted slightly longer, leading to a significant difference in time-corrected $AUEC_{0\text{-}6hr}$ (table 1).

FIGURE 1 **Average drug concentration profiles (mean + SD) of MRLA023 0.5mg (□), MRLA023 1.5mg (○) and lorazepam 2mg (Δ) after oral administration**

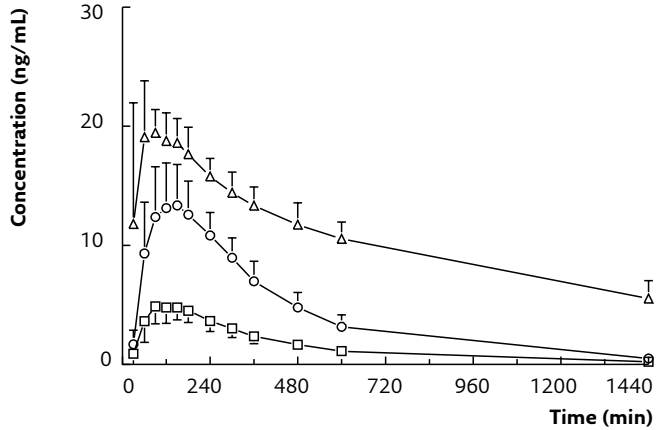
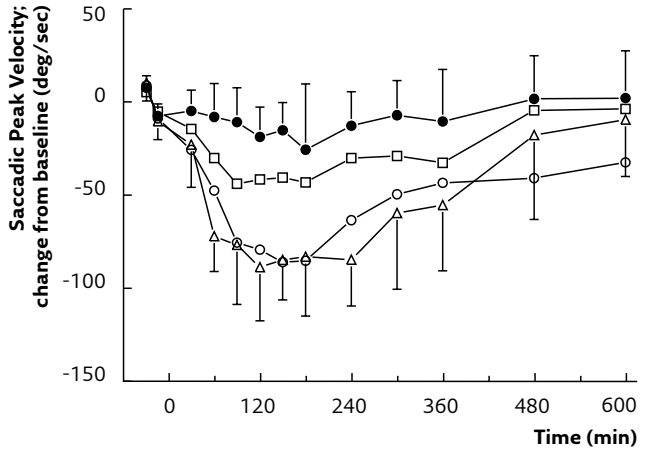


FIGURE 2 **Average time profile (mean + SD) of Saccadic Peak Velocity (change from baseline) after oral administration of placebo (●), MRLA023 0.5mg (□), MRLA023 1.5mg (○) and lorazepam 2mg (Δ)**

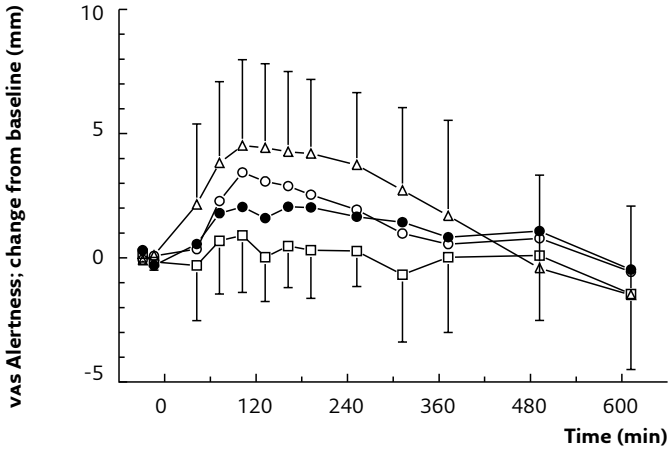


VISUAL ANALOGUE SCALE The VAS score of alertness, which was used to estimate subjective sedative effects, only showed a significant average effect after lorazepam (table 1). The average curve for the high dose of MRLA023 was in between the average curves of lorazepam and placebo (figure 3), and consequently, the $AUC_{0\text{-}6hr}$ of the high dose of MRLA023 did not differ significantly from either lorazepam or placebo. Subjective calmness was reduced after the high dose of MRLA023, while none of the other treatments showed any effect. No significant effects were observed for the VAS contentedness subscale.

TABLE 1 **Pharmacodynamic measurements $AUC_{0\text{-}6hr}$ relative to baseline: Saccadic Eye Movements, Visual Analogue Scales and Body Sway; ANOVA results (contrast, 95% CI, p-value)**

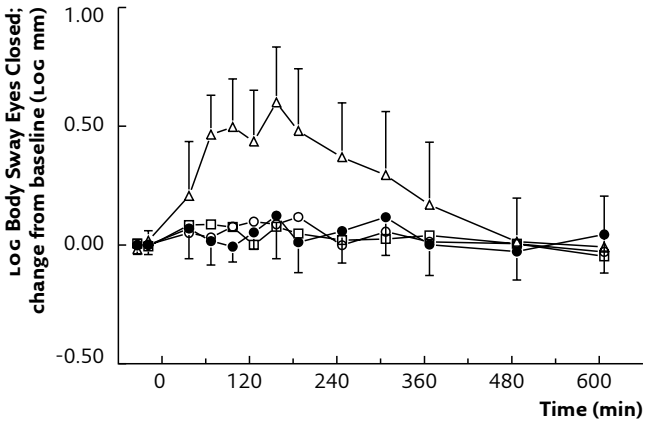
Variable	Overall treatment effect (p-value)	Placebo MRLA023 0.5mg	Placebo MRLA023 1.5mg	Lorazepam 2mg MRLA023 1.5mg	Placebo Lorazepam 2mg
Saccadic Peak Velocity (deg/sec)	<.0001	21.58 (8.40 / 34.76) p = 0.002	45.24 (32.06 / 58.42) p < 0.001	-13.99 (-27.17 / -0.81) p = 0.038	59.23 (46.05 / 72.41) p < 0.001
Saccadic Latency (sec)	0.0003	-0.002 (-0.014 / 0.009) p = 0.672	-0.009 (-0.021 / 0.002) p = 0.116	0.017 (0.006 / 0.029) p = 0.005	-0.027 (-0.039 /-0.015) p < 0.001
Saccadic Inaccuracy (%)	0.0008	-0.09 (-1.27 / 1.08) p = 0.874	-0.03 (-1.21 / 1.14) p = 0.954	2.21 (1.03 / 3.38) p < 0.001	-2.24 (-3.42 / -1.07) p < 0.001
VAS Alertness (ln mm)	0.0082	1.35 (-0.37 / 3.08) p = 0.119	-0.33 (-2.05 / 1.39) p = 0.698	1.47 (-0.25 / 3.19) p = 0.092	-1.80 (-3.52 /-0.08) p = 0.041
VAS Contentedness (ln mm)	0.2630	-0.25 (-0.97 / 0.48) p = 0.492	-0.71 (-1.44 / 0.02) p = 0.055	-0.47 (-1.20 / 0.25) p = 0.193	-0.24 (-0.96 / 0.49) p = 0.510
VAS Calmness (ln mm)	0.0097	-0.14 (-0.46 / 0.17) p = 0.355	-0.53 (-0.84 /-0.22) p = 0.002	-0.43 (-0.74 /-0.12) p = 0.009	-0.10 (-0.41 / 0.22) p = 0.529
Log Body Sway Eyes Closed (log mm)	<.0001	0.009 (-0.087 / 0.106) p = 0.849	-0.001 (-0.098 / 0.095) p = 0.976	0.310 (0.214 / 0.407) p < 0.001	-0.312 (-0.408 /-0.215) p < 0.001
Log Body Sway Eyes Open (log mm)	<.0001	-0.026 (-0.102 / 0.050) p = 0.487	-0.021 (-0.097 / 0.055) p = 0.575	0.267 (0.192 / 0.343) p < 0.001	-0.288 (-0.364 /-0.213) p < 0.001

FIGURE 3 **Average time profile (mean + SD) of VAS Alertness (change from baseline) after oral administration of placebo (●), MRLA023 0.5mg (□), MRLA023 1.5mg (○) and lorazepam 2mg (Δ)**



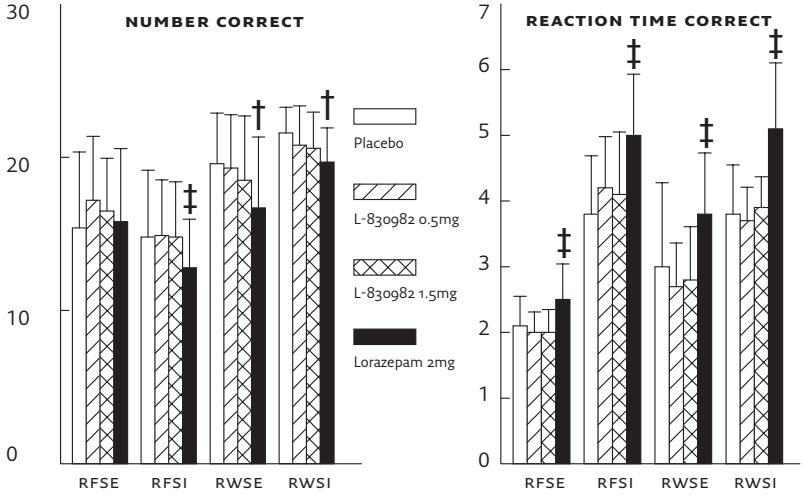
BODY SWAY No body instability was observed after either dose of MRLA023 compared to placebo (figure 4). Lorazepam, however, caused a profound and highly significant increase in body sway (table 1).

FIGURE 4 **Average time profile (mean + SD) of LOG Body Sway Eyes Closed (change from baseline) after oral administration of placebo (●), MRLA023 0.5mg (□), MRLA023 1.5mg (○) and lorazepam 2mg (Δ)**



COGNITIVE FUNCTION TESTS AND CORSI BLOCK TAPPING TASK Three of the four recognition tests revealed that lorazepam caused significant memory impairment, compared to placebo (figure 5). In contrast, neither dose of MRLA023 showed any significant effect on memory. Aside from the effects of lorazepam on the ability to answer correctly, it also significantly increased the reaction times to the correct answers of all memory tests with a range of 0.5-1.3 sec from placebo (figure 5). These significantly higher reaction times were not found with MRLA023. No treatment effects were observed on the Corsi block tapping task.

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 MRLA023 1.5mg**

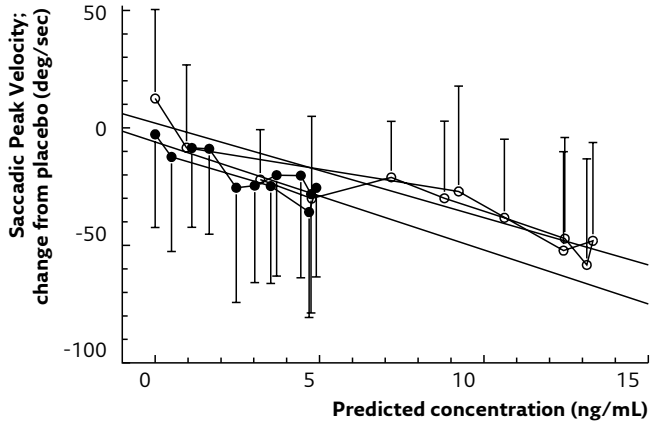


Pharmacokinetic/pharmacodynamic relationships (PK/PD)

Concentration-effect-relationships were only determined for statistically significant pharmacodynamic effects of MRLA023 (*ie* only for SPV). The average PK/PD relationship between the changes in SPV from baseline and the predicted concentration for both doses of MRLA023 is represented in figure 6. A linear concentration-effect model was estimated without an effect

compartment for both doses of MRLA023. Both slope and intercept for SPV did not differ significantly between the two doses of MRLA023. There were no obvious signs of hysteresis or maximum effects. Individual graphs indicated that no improvement could be obtained using either a more complex concentration-effect model or an effect compartment.

FIGURE 6 **Concentration-effect profiles for Saccadic Peak Velocity of MRLA023 0.5mg (●) and MRLA023 1.5mg (○)**



Discussion

The current placebo-controlled study in healthy male volunteers investigated the effects of two doses of MRLA023, a $GABA_A$ $\alpha_{2,3}$ subtype selective partial agonist. The benzodiazepine lorazepam was used in a therapeutic anxiolytic dose as a positive control. As expected, lorazepam caused sedation (shown by SPV-decreases and VAS-effects), impairment of memory and body sway. These effects are typical for benzodiazepines, and are often used as indicators of the drug's effects. MRLA023 caused dose dependent SPV-effects of a similar magnitude as lorazepam, but MRLA023 had no detectable effects on VAS alertness score, memory or postural stability.

ref. 12-13

The results from the current study suggest that the clinical effects of MRLA023 may differ from those of lorazepam, but this relies on the assumption that equipotent therapeutic doses were used. Therapeutic equipotency cannot be proven at this stage, because the clinical effects

of MRLA023 have not yet been determined in patients with anxiety. However, lorazepam 2 mg and the highest dose of MRLA023 caused similar reductions in Saccadic Peak Velocity (SPV). Although a decrease in SPV is usually viewed as a biomarker for sedation, a recent review showed that the SPV-effect is also closely linked to therapeutic levels of benzodiazepines. If the clear SPV-reductions with MRLA023 and lorazepam are indicative of the therapeutic dose, MRLA023 would be expected to have fewer of the adverse effects in patients that are typically associated with non selective benzodiazepines like lorazepam. Clinical studies are needed to confirm that MRLA023 has similar efficacy but fewer adverse effects than lorazepam in patients with generalised anxiety disorder. In any case, the CNS-effect profile of the selective partial GABA-agonist MRLA023 in healthy humans differs from that of the non-selective agonist lorazepam.

ref. 20
ref. 9

Although direct comparative studies are rare, non-selective benzodiazepines, like diazepam, zopiclone, flurazepam, lormetazepam, triazolam, temazepam and lorazepam, all show comparable effects on memory, alertness and postural stability. This suggests that the differentiation between MRLA023 and lorazepam, observed in the current study, could be related to the differences in GABA-subtype (non-) selectivity. It is reported that the effects of benzodiazepines are mediated by specific $GABA_A$ receptor subtypes. The α_1 sub-unit is believed to primarily mediate the sedative properties and as a consequence, potentially mediate memory properties of $GABA_A$ agonists. The selective α_1-agonist zolpidem causes clear SPV-reductions and is used as a hypnotic agent. The current study supports the link between the α_1 sub-unit and sedation. MRLA023 is a $GABA_A$ partial $\alpha_{2,3}$ agonist devoid of α_1-activity in pre-clinical experiments. MRLA023 causes no memory impairment and less subjective sedation than the non-selective full benzodiazepine-agonist lorazepam. However, preclinical evidence also suggests that the α_2,α_3 and α_5 sub-units mediate the therapeutic, myorelaxation and motor impairment properties of $GABA_A$ agonists. In view of this, MRLA023 shows a surprising lack of motor impairment. There are several explanations. It could reflect the partial agonist character of the MRLA023. The purported α_2,α_3-effect of MRLA023 may become more apparent at higher doses, not evaluated in this study. Finally, the pre-clinical subselectivity may not always show the same pattern in humans.

ref. 21-26
ref. 4
ref. 27

Previous studies with other partial $GABA_A$ agonists showed less differentiating effects than MRLA023. However, these agents show no subtype selectivity. Bretazenil, for example, showed differences from placebo in saccadic peak velocity, body sway and the VAS score of alertness. This could be due to

ref. 21

the difference in selectivity for different subtypes compared with MRLA023, because bretazenil is generally less potent on all α-subtypes than a full agonist like diazepam. Ro 41-3696, reported to be a partial agonist, induced fewer effects on psychomotor performance and memory than 10 mg zolpidem at 1.5 h after intake but the effects were still significantly greater than placebo. Moreover, it is unknown whether these doses were equipotent, an important requisite for comparison of partial agonism and subtype selectivity.

ref. 28

ref. 29

In conclusion, this study showed a clear differentiation in pharmacodynamic effects for the selective $GABA_A$ agonist MRLA023, which was not found for the non-selective benzodiazepine lorazepam. This differentiation may be related to selectivity for different $GABA_A$ receptor subtypes, which may be associated with fewer side effects at therapeutically effective doses in patients.

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