Received: 24 March 2021 | Revised: 20 May 2021 | Accepted: 3 August 2021

DOI: 10.1111/cts.13145

ARTICLE

A randomized, multicenter trial assessing the effects of rapastinel compared to ketamine, alprazolam, and placebo on simulated driving performance

Shengfang Su[1] | **Gary Kay**[2] | **Thomas Hochadel**[2] | **Jonathan Rojo**[1] | **J. Christopher Stein**[1] | **Ramesh Boinpally**[3] | **Antonia Periclou**[1]

[1]Allergan plc (now AbbVie, Inc.), Madison, New Jersey, USA

[2]Cognitive Research Corporation, St. Petersburg, Florida, USA

[3]Clinical Pharmacology, AbbVie, Inc., Madison, New Jersey, USA

Correspondence
Ramesh Boinpally, Clinical Pharmacology, AbbVie, Inc., 5 Giralda Farms, Madison, NJ, 07940, USA.
Email: ramesh.boinpally@abbvie.com

Funding information
These studies and data analysis were supported by funding from Allergan plc (now AbbVie). Allergan plc (now AbbVie) was involved in the study design, and data collection, analysis and interpretation of data, and decision to present these results.

Abstract

N-methyl-D-aspartate ionotropic glutamatergic receptor (NMDAR) modulators, including rapastinel and ketamine, elicit rapid and sustained antidepressant responses in patients with treatment-resistant major depressive disorder. This phase I, randomized, multicenter, placebo-controlled, five-period, crossover, single-dose study evaluated simulated driving performance of healthy participants ($N = 107$) after single doses of rapastinel slow intravenous (i.v.) bolus 900 and 1800 mg, alprazolam oral 0.75 mg (positive control), ketamine i.v. infusion 0.5 mg/kg (clinical comparator), and placebo ~ 45 min before driving. The primary end point was SD of lateral position (SDLP) during the 60-min 100-km simulated driving scenario. Additional measures of driving performance, sleepiness, and cognition were also evaluated. To assess effects over time, mean SDLP was calculated for each 10-min interval of driving. Sensitivity of the assays was confirmed with alprazolam (all placebo comparisons $p < 0.02$). Rapastinel 900 and 1800 mg did not significantly affect simulated driving performance compared to placebo (both $p > 0.5$). Both rapastinel doses resulted in significantly less impaired driving compared to alprazolam or ketamine (all $p < 0.002$); ketamine significantly impaired driving compared to placebo ($p = 0.0001$). Results for the additional measures were similar to the primary end point. No new safety signals were observed for any study interventions. This first study of rapastinel effects on simulated driving found that rapastinel 900 and 1800 mg did not impair driving performance, but ketamine 0.5 mg/kg resulted in significantly impaired driving performance. Ketamine's effects on driving were maintained for at least 105 min, indicating that clinicians should be vigilant to prevent or postpone driving in patients after ketamine treatment.

Shengfang Su, Jonathan Rojo, J. Christopher Stein, and Antonia Periclou: Were full-time employees at Allergan plc (now AbbVie, Inc.) at the time of the study.

Clinical Trials Registry: NCT03814733 at ClinicalTrials.gov.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Prior to this current study, the effects of rapastinel, an N-methyl-D-aspartate ionotropic glutamatergic receptor (NMDAR) modulator, on driving performance were unknown. Ketamine, a current treatment for major depressive disorder, also an NMDAR modulator, has previously been shown to impair driving. Its effects have not been investigated in a large placebo-controlled randomized control trial or over multiple time points following dosing.

WHAT QUESTION DID THIS STUDY ADDRESS?

What are the effects of rapastinel compared to placebo and ketamine on driving performance and driving-related measures?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This is the first study investigating the effects of rapastinel on driving performance that showed single doses of rapastinel (900 or 1800 mg) did not impair driving performance or affect driving-related measures compared to placebo. An i.v. infusion of ketamine 0.5 mg/kg impaired driving and related measures for up to 105 min following dosing when compared to placebo, rapastinel 900 mg, and rapastinel 1800 mg.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Clinicians will become aware of the risk of impaired driving in patients treated with ketamine.

INTRODUCTION

Major depressive disorder (MDD) is a prevalent and disabling disease. Worldwide, MDD affects 322 million people (4.4% of the population)[1] and is the leading cause of disability.[2] In the United States, MDD is the leading cause of disability in persons aged 15–44 years.[3] Approximately 30% of patients with MDD are not adequately treated with antidepressants[4]; inadequate treatment can impair quality of life.[5]

Current US Food and Drug Administration (FDA)-approved antidepressants, which primarily act through monoaminergic modulation,[6] can take weeks to elicit response.[7] Even after treatment with monoamine antidepressants, a subpopulation of patients are resistant to treatment.[8] N-methyl-D-aspartate ionotropic glutamatergic receptor (NMDAR) modulation can elicit rapid and sustained antidepressant response.[9] Two NMDAR modulators, ketamine [2-(2-chlorophenyl)-2-(methylamino) cyclohexanone] and rapastinel (GLYX-13), act through noncompetitive antagonism and positive allosteric modulation, respectively. Ketamine has been shown to elicit response in patients with treatment-resistant MDD in phase III trials, but it is associated with dissociative, analgesic, and psychotomimetic effects.[10] In preclinical and phase II studies, rapastinel produced antidepressant effects without psychotomimetic or dissociative effects.[11,12]

Driving requires functioning in multiple cognitive and sensory domains, including visual tracking, time perception, and attention.[13] Ketamine has been shown to affect each of these individual domains and consequently has been detected in 45% of intoxicated drivers involved in nonfatal accidents and 9% involved in fatal accidents in Hong Kong.[14] In a small, open-label simulated driving study, ketamine significantly impaired driving performance.[15] The highest dose of ketamine assessed in that study was similar to a blood alcohol content (BAC) of 0.15%, but direct comparisons between ketamine and alcohol were not made. To our knowledge, this is the first study to assess the effects of ketamine on multiple driving performance parameters in a large randomized, double-blind, placebo-controlled trial.

The effects of rapastinel on driving performance is thus far unknown; characterizing these effects is important because rapastinel is a psychoactive drug that modulates the same receptor target as ketamine that is known to negatively affect driving ability. Here, we evaluate the acute and residual effects of rapastinel, ketamine (clinical comparator), alprazolam (positive control), and placebo on driving performance in healthy adult participants using a 60-min driving simulation; additional measures of safety, cognition, and driving ability are also assessed.

METHODS

This phase I, randomized, multicenter, double-blind, double-dummy, placebo-controlled, five-period, crossover,

single-dose study evaluated the driving performance of healthy participants after single doses of rapastinel slow intravenous (i.v.) bolus 900 and 1800 mg, alprazolam oral 0.75 mg, ketamine i.v. infusion 0.5 mg/kg over 40 min, and placebo. The study was conducted at two study centers in the United States and Canada. The final study protocol was approved by institutional review boards for the site in the US site or by ethics committees and government agencies for the site in Canada. Participants were screened and recruited in compliance with the International Conference on Harmonization Good Clinical Practice Guideline and the Declaration of Helsinki and provided written informed consent after receiving a complete description of the study.

Participants

Healthy males and female subjects 21 to 65 years of age (inclusive) with a body mass index of 18 to 32 kg/m^2 (inclusive) were enrolled. Participants were screened within 28 days of study intervention administration. Participants were required to hold a valid driver's license, to not show evidence of simulator sickness on the Simulator Sickness Questionnaire, and to have a regular sleep pattern with no report of daytime sleepiness (score <10 on the Epworth Sleepiness Scale).[16] Use of concomitant medications, except progesterone-only birth control or hormone-replacement therapy (female participants), was prohibited. Participants with a screening or baseline Columbia-Suicide Severity Rating Scale (C-SSRS)[17] response indicating any current suicidal ideation or a history of active suicidal ideation within the past 6 months, suicide attempts within the past year, or those considered a suicide risk were excluded. Participants with sleep disorders/conditions or visual/auditory impairment with the potential to interfere with study conduct were prohibited from entering the study.

Participants were nonsmoking and nonusers of nicotine-containing and caffeine-containing products; alcoholic beverages were restricted the days before admission to the study center.

Study interventions

Participants were admitted on day −1 of each period to complete safety evaluations, the CogScreen Symbol Digit Coding (SDC) test,[18] and training/practice on the Country Vigilance-Divided Attention (CVDA) driving scenario on the Cognitive Research Corporation Driving Simulator-MiniSim (CRCDS-MiniSim; Cognitive Research Corporation, St. Petersburg, FL). The CVDA driving scenario is a 100-kilometer, monotonous, two-lane, highway driving scenario with proven sensitivity to sleepiness and central nervous system effects.[19]

Participants were randomly assigned to one of 10 intervention sequences to receive all five study interventions (Table 1): rapastinel (900 and 1800 mg), alprazolam (0.75 mg) as a positive control, ketamine (0.5 mg/kg) as a clinical comparator, and placebo. Study interventions were administered after a fasting period of at least 2 h using the following standardized administration protocol: participants received an oral dose of alprazolam or matching placebo followed immediately by a 40-min i.v. infusion of ketamine or matching placebo, and then a slow i.v. bolus of rapastinel (900 or 1800 mg administered in 2–4 450-mg prefilled syringes injected at a rate of ~ 1 min [±3 s] per syringe) or matching placebo.

Thirty minutes after completion of slow bolus i.v. rapastinel or placebo dosing (32–34 min post-ketamine or 72–74 min post-alprazolam), nondriving assessments addressing self-reported sleepiness and readiness to drive were performed. The 60-min driving simulation was carried out ~ 45 min post-slow i.v. rapastinel or placebo bolus (47–49 min post-ketamine or 87–89 min post-alprazolam) and was followed by queries addressing self-appraisal of motivation and driving performance using a visual analog scale (VAS). Each intervention was separated by a washout period of 6–14 days, which could be extended to 21 days, allowing for the elimination of rapastinel (terminal half life [$T_{1/2}$]: <10 min),[11] alprazolam ($T_{1/2}$: 11.2 h),[20] and ketamine ($T_{1/2}$: 2.5–3 h).[21]

Dose selection of study interventions

Rapastinel doses selected for assessment in the study were the highest potential therapeutic dose (900 mg, roughly equivalent to the 10 mg/kg dose used in the phase II proof of concept trial)[22] and double the highest potential therapeutic dose (1800 mg), which aligns with the current FDA guidance for evaluating a drug's effects on driving.[23] Rapastinel has a short elimination half-life of less than 10 min.[11] Alprazolam 0.75 mg was selected as a positive control because a 1.0 mg dose has comparable effects on driving as a BAC of greater than 0.15% in the same driving simulator and scenario[24] and 0.5 mg is the lowest dose that impairs cognitive and psychomotor performance,[25] so the median dose was chosen. After oral administration, plasma concentrations of alprazolam peak within 1–2 h with an elimination half-life of ~ 11.2 h.[20] The ketamine dose 0.5 mg/kg was selected as a clinical comparator because it has demonstrated antidepressant effects in a phase III clinical trial.[26] Intravenous ketamine elicits first effects within seconds and has an elimination half-life of ~ 2.5–3 h.[21]

TABLE 1 Intervention sequences

	Period 1	Period 2	Period 3	Period 4	Period 5
Sequence 1	Rapastinel 900 mg	Rapastinel 1800 mg	Placebo	Ketamine 0.5 mg/kg	Alprazolam 0.75 mg
Sequence 2	Rapastinel 1800 mg	Ketamine 0.5 mg/kg	Rapastinel 900 mg	Alprazolam 0.75 mg	Placebo
Sequence 3	Ketamine 0.5 mg/kg	Alprazolam 0.75 mg	Rapastinel 1800 mg	Placebo	Ketamine 0.5 mg/kg
Sequence 4	Alprazolam 0.75 mg	Placebo	Ketamine 0.5 mg/kg	Rapastinel 900 mg	Rapastinel 1800 mg
Sequence 5	Placebo	Rapastinel 900 mg	Alprazolam 0.75 mg	Rapastinel 1800 mg	Ketamine 0.5 mg/kg
Sequence 6	Alprazolam 0.75 mg	Placebo	Ketamine 0.5 mg/kg	Rapastinel 1800 mg	Rapastinel 900 mg
Sequence 7	Placebo	Alprazolam 0.75 mg	Rapastinel 900 mg	Ketamine 0.5 mg/kg	Rapastinel 1800 mg
Sequence 8	Rapastinel 900 mg	Placebo	Rapastinel 1800 mg	Alprazolam 0.75 mg	Ketamine 0.5 mg/kg
Sequence 9	Rapastinel 1800 mg	Rapastinel 900 mg	Ketamine 0.5 mg/kg	Placebo	Alprazolam 0.75 mg
Sequence 10	Ketamine 0.5 mg/kg	Rapastinel 1800 mg	Alprazolam 0.75 mg	Rapastinel 900 mg	Placebo

Primary and key secondary end points

The primary end point of the study was the SDs of lateral position (SDLP) in the simulated driving scenario after single i.v. doses of rapastinel 900 mg and rapastinel 1800 mg compared to placebo and alprazolam 0.75 mg. A noninferiority threshold of 4.4 cm SDLP, equivalent to the difference between placebo and a BAC of 0.05% for the CVDA CRCDS-MiniSim, was prespecified.[27] The key secondary end points were SDLP differences following rapastinel versus ketamine 0.5 mg/kg dosing.

Additional secondary end points

Additional secondary end points included other measures of driving performance, the CogScreen SDC test, and self-report measures. These driving measures included the number of lane exceedances, lane exceedance maximums (maximum lateral deviation from the lane center), duration of exceedance, and total number of collisions. The CogScreen SDC test is a computer-administered digit-symbol substitution test that measures changes in attention processing speed, visual scanning, working memory, and speed of information processing. The principal SDC result is the number of correct responses (in 120 s); other results include the percentage of correct responses (i.e., accuracy) and the SD of reaction time. Self-report measures included a self-rating of safety to drive (participants were asked "Right now do you feel safe to drive?"), motivation and driving performance (assessed using a VAS), and sleepiness (measured with the Karolinska Sleepiness Scale [KSS]).[18,28]

Ad hoc analyses

To investigate the effects of each intervention throughout the driving simulation, the mean SDLP was determined for each 10-min interval of the drive (i.e., 0–10 min, 10–20 min, etc.) and plotted as a function of time.

Statistical analyses

This study is designed to test noninferiority of rapastinel (900 mg) relative to placebo and subsequently rapastinel (1800 mg) relative to placebo, with an alprazolam test versus placebo to confirm the sensitivity of the simulator to detect intervention effects. The following assumptions were made in the sample size computation: (a) SD of differences between rapastinel and placebo within participant for SDLP is ~ 9.5 cm; (b) the true difference between rapastinel doses and placebo is 0; and (c) the noninferiority margin is proposed to be 4.4 cm, which is the effect seen with a BAC of 0.05%.[27] Under these assumptions, a sample of 80 participants would provide greater than 90% power to establish noninferiority of either dose of rapastinel compared to placebo in terms of the primary end point, SDLP. This sample size is more than

adequate to detect alprazolam differences, which are anticipated to exceed the noninferiority margin, from placebo.

The primary end point was analyzed using a mixed-model for repeated measures with fixed effects for sequence, period, and intervention, with repeated observations for participants. Pairwise, within-participant differences in SDLP were compared for symmetry using the McNemar test. Pairwise differences were also analyzed to determine the number of participants with SDLP scores exceeding 4.4 cm. The secondary end points were evaluated using a similar mixed model as the primary end point, except for lane exceedance number, which was log-transformed before analysis.

Safety

Adverse events (AEs), serious AEs (SAEs), C-SSRS results, pulse oximetry, clinical laboratory findings, electrocardiogram (ECG) data, physical examinations, and vital signs were monitored.

RESULTS

Study participants

Of 107 randomized participants, 97 (90.7%) completed the study. Participant demographic characteristics are listed in Table 2.

Primary and key secondary end points

Primary and key secondary results are listed in Table 3. One participant exhibited impaired driving during the practice drive (predosing) and was therefore excluded from pharmacodynamic analysis. The sensitivity of the assay was confirmed by significantly worse SDLP for alprazolam 0.75 mg versus placebo (least-squares mean difference [LSMD] = 19.44 cm, 95% confidence interval [CI]: 17.44, 21.45; $p < 0.0001$) and the upper limit of the 95% CI was greater than the prespecified noninferiority criterion of 4.4 cm (based on a BAC of 0.05% that is known to impair driving).[27] Within-participant differences in SDLP between alprazolam 0.75 mg and placebo in the symmetry analysis were not symmetric about zero (i.e., McNemar value >7.53). For the primary end point, SDLP, there were no significant differences for rapastinel 900 mg or rapastinel 1800 mg versus placebo (900 mg: LSMD = −0.22 cm, 95% CI: −2.19, 1.76; $p = 0.8294$ and 1800 mg: LSMD = 0.79 cm, 95% CI: −1.26, 2.84; $p = 0.4486$). The upper limits of the 95% CIs for rapastinel 900 mg and 1800 mg versus placebo did not exceed the pre-established noninferiority criterion. The distribution of within-participant differences between rapastinel 900 or 1800 mg and placebo in the symmetry analysis were symmetric about zero (Maximum McNemar Statistic <7.562 and <7.538, respectively).

Dosing with rapastinel 900 or 1800 mg resulted in significantly better driving performance compared to

TABLE 2 Participant disposition and baseline demographics (safety population)

	Rapastinel 900 mg (*N* = 101)	Rapastinel 1800 mg (*N* = 102)	Ketamine 0.5 mg/kg (*N* = 103)	Alprazolam 0.75 mg (*N* = 100)	Placebo (*N* = 101)
Age (years)					
Mean (SD)	38.1 (10.52)	38.3 (10.35)	38.1 (10.41)	38.1 (10.44)	37.9 (10.57)
Median	36.0	36.5	36.0	36.0	36.0
Range	21–59	21–50	21–50	22–59	21–59
Gender, *n* (%)					
Male	60 (59.4)	61 (59.8)	61 (59.2)	59 (59.0)	60 (59.4)
Female	41 (40.6)	41 (40.2)	42 (40.8)	41 (41.0)	41 (40.6)
Race, *n* (%)					
White	81 (80.2)	82 (80.4)	81 (78.6)	80 (80.0)	80 (79.2)
Black or African American	14 (13.9)	14 (13.7)	16 (15.5)	14 (14.0)	15 (14.9)
Native Hawaiian or Other Pacific Islander	2 (2.0)	2 (2.0)	2 (1.9)	2 (2.0)	2 (2.0)
Asian	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.0)
Other	3 (3.0)	3 (2.9)	3 (2.9)	3 (3.0)	3 (3.0)
Ethnicity, *n* (%)					
Hispanic or Latino	17 (16.8)	17 (16.7)	17 (16.5)	16 (16.0)	17 (16.8)
Not Hispanic or Latino	84 (83.2)	85 (83.3)	86 (83.5)	84 (84.0)	84 (83.2)

Note: Safety population includes all participants who received/took ≥1 administration of study intervention.

TABLE 3 Primary and key secondary end points – Standard deviation of lane position

	RAP 900 mg (*N* = 101)	RAP 1800 mg (*N* = 102)	KET 0.5mg/kg (*N* = 103)	Alprazolam 0.75 mg (*N* = 100)	Placebo (*N* = 101)
N	100	101	97	96	100
CM, mean (SD)	31.20 (7.233)	32.31 (8.450)	35.74 (10.273)	50.70 (15.608)	31.77 (7.776)
CM, LS means*	31.37	32.37	35.66	51.03	31.58
p value for period*					0.1740
p value for sequence*					0.2062
	RAP 900 mg vs. placebo	**RAP 1800 mg vs. placebo**		**Alprazolam 0.75 mg vs. placebo**	
Primary comparisons					
Difference in LS means*	−0.22	0.79		19.44	
95% CI*	(−2.19, 1.76)	(−1.26, 2.84)		(17.44, 21.45)	
p value*	0.8294	0.4486		<0.0001	
	RAP 900 mg vs. KET 0.5 mg/kg	**RAP 1800 mg vs. KET 0.5 mg/kg**		**KET 0.5 mg/kg vs. placebo**	
Key secondary comparisons					
Difference in LS means*	−4.30	−3.29		4.08	
95% CI*	(−6.35, −2.24)	(−5.28, −1.30)		(2.02, 6.14)	
p value*	<0.0001	0.0012		0.0001	

Note: One participant was excluded from the analyses.

Abbreviations: CI, confidence interval; CM, centimeter; KET, ketamine; LS, least squares; RAP, rapastinel; SD, standard deviation.

*Mixed-effects model with fixed effects for sequence, period, and treatment, with repeated observations based on an unstructured covariance structure and Kenward-Roger degrees of freedom. The *p* value tests the null hypothesis that the difference in LS means = 0 versus the alternative hypothesis that the difference in LS means ≠ 0. Estimated differences are the first treatment label listed minus the second treatment label.

alprazolam 0.75 mg (SDLP 900 mg: LSMD = −19.66 cm, 95% CI: −21.72, −17.60; $p < 0.0001$ and SDLP 1800 mg: LSMD = −18.65 cm, 95% CI: −20.72, −16.59; $p < 0.0001$). Mean SDLP was significantly worse for ketamine 0.5 mg/kg versus placebo (LSMD = 4.08 cm, 95% CI: 2.02, 6.14; $p = 0.0001$) and the upper-limit of the 95% CI exceeded the noninferiority criterion. Following intervention with rapastinel 900 or 1800 mg, participants maintained their lane position significantly better than with ketamine 0.5 mg/kg (900 mg: LSMD = −4.30 cm, 95% CI: −6.35, −2.24; $p < 0.0001$ and 1800 mg: LSMD = −3.29 cm, 95% CI: −5.28, −1.30; $p = 0.0012$).

Ad hoc analyses

For the SDLP time-course analysis, results indicated that 10 participants in the 50–60 min time bin completed the drive in less than 60 min due to driving at an increased rate of speed (2 each in the rapastinel 900 and 1800 mg groups and 3 each in the ketamine 0.5 mg/kg and alprazolam 0.5 mg/kg groups). Results were calculated using the drive data up to the completed time interval. Exclusion of the results for participants completing the drive before the 60th minute had no apparent impact on outcomes.

In the first 10-min interval, no significant differences in driving performance occurred in rapastinel 900 mg or rapastinel 1800 mg compared to placebo groups (900 mg: LSMD = −0.88 cm, 95% CI: −2.51, 0.76; $p = 0.291$ and 1800 mg: LSMD = −0.28 cm, 95% CI: −1.97, 1.41; $p = 0.745$) and neither upper limit of the two-sided 95% CIs exceeded the pre-established noninferiority criterion. In the same interval, lane position was maintained significantly better following rapastinel 900 or 1800 mg dosing compared to ketamine 0.5 mg/kg dosing (900 mg: LSMD = −3.59 cm, 95% CI: −5.29, −1.89; $p<0.0001$ and 1800 mg: LSMD = −2.99, 95% CI: −4.64, −1.34; $p = 0.0004$). No significant differences occurred for either dose of rapastinel versus placebo for the remaining time intervals. Rapastinel 900 or 1800 mg dosing compared to ketamine 0.5 mg/kg dosing resulted in significantly improved lane maintenance for all time intervals, except for the differences between rapastinel 1800 mg and ketamine 0.5 mg/kg in the 10–20 and 50–60 min intervals (LSMD = −2.15, 95% CI: −4.35, 0.01; $p = 0.0554$ and LSMD = −2.04, 95% CI: −4.35, 0.27; $p = 0.0839$, respectively). For ketamine 0.5 mg/kg, the highest SDLP

TABLE 4 Other measures of simulated driving performance

	RAP 900 mg (*N* = 101)	RAP 1800 mg (*N* = 102)	KET 0.5 mg/kg (*N* = 103)	Alprazolam 0.75 mg (*N* = 100)	Placebo (*N* = 101)
N	100	101	97	96	100
Number of lane exceedances (*n*)[a]					
Mean (SD)	2.67 (1.324)	2.81 (1.396)	3.33 (1.343)	4.74 (0.994)	2.80 (1.361)
LS means[b]	2.70	2.82	3.32	4.77	2.81
Maximum lane exceedance (cm)[c]					
Mean (SD)	69.55 (96.237)	79.04 (102.498)	111.95 (131.219)	306.80 (187.667)	66.30 (68.582)
LS means[b]	71.38	82.39	108.78	310.91	67.62
Duration of lane exceedance (s)[d]					
Mean (SD)	42.51 (76.860)	53.49 (100.402)	103.05 (173.531)	327.96 (280.929)	49.82 (88.448)
LS means[b]	45.07	56.07	97.14	329.48	51.73
Total collisions (*n*)[e]					
Mean (SD)	0.2 (0.87)	0.3 (1.02)	0.6 (1.82)	6.1 (8.55)	0.2 (0.73)

	RAP 900 mg vs. placebo	RAP 1800 mg vs. placebo	RAP 900 mg vs. KET 0.5 mg/kg	RAP 1800 mg vs. KET 0.5 mg/kg	KET 0.5 mg/kg vs. placebo	Alprazolam 0.75 mg vs. placebo
Number of lane exceedances (*n*)						
LSMD (95% CI)[b]	−0.11 (−0.34, 0.12)	0.01 (−0.22, 0.24)	−0.62 (−0.86, −0.39)	−0.51 (−0.74, −0.28)	0.51 (0.28, 0.75)	1.96 (1.73, 2.19)
P value[b]	0.3460	0.9605	<0.0001	<0.0001	<0.0001	<0.0001
Maximum lane exceedance (cm)						
LSMD (95% CI)[b]	3.76 (−26.33, 33.86)	14.77 (−13.81, 43.35)	−37.40 (−66.24, −8.56)	−26.39 (−56.56, 3.78)	41.16 (12.42, 69.89)	243.29 (212.85, 273.73)
p value[b]	0.8058	0.3101	0.0112	0.0862	0.0051	<0.0001
Duration of lane exceedance (s)						
LSMD (95% CI)[b]	−6.66 (−42.97, 29.64)	4.340 (−33.78, 42.47)	−52.07 (−90.32, −13.82)	−41.07 (−77.55, −4.59)	45.41 (7.07, 83.75)	277.76 (240.88, 314.63)
p value[b]	0.7183	0.8228	0.0078	0.0275	0.0204	<0.0001
Differences in number of collisions (n)						
Mean (SD)	0.00 (1.079)	0.10 (0.823)	−0.36 (1.591)	−0.39 (1.832)	0.36 (1.701)	5.94 (8.493)
p value[f]	0.8188	0.3091	0.0223	0.0398	0.0425	<0.0001

Note: One participant was excluded from the analyses.

Abbreviations: CI, confidence interval; LSMD, least square mean difference; KET, ketamine; RAP, rapastinel; SD, standard deviation.

[a]Lane exceedance number was log-transformed as ln[x + 1].

[b]Mixed-effects model with fixed effects for sequence, period, and treatment, with repeated observations based on an unstructured covariance structure, and Kenward-Roger degrees of freedom. The *p* value tests the null hypothesis that the difference in LS means = 0 versus the alternative hypothesis that the difference in LS means ≠ 0. Estimated differences are the first treatment label listed minus the second treatment label.

[c]Measure of lane exceedance severity in centimeters. Measures the maximum lateral deviation that driver's vehicle travels from the center of the lane.

[d]Measure of the amount of time that the driver takes to make corrections to bring the vehicle back into the lane of travel (in seconds). It is calculated by summing the total amount of time that any part of a vehicle spends outside the left or right lane boundaries.

[e]Total number of collisions is the summation of the following: Total number of times (over the entire scenario) that the vehicle collided with another vehicle or roadway object in the scene or went off the lane/road (i.e., [lane deviation] + [half of the vehicle's width] > [lane width / 2] + 5.0) and, therefore, presumably crashed.

[f]From Wilcoxon Signed Rank test.

occurred in the 30–40 min time interval (37.76 cm). Slight increases in SDLP occurred in the rapastinel 900 mg, rapastinel 1800 mg, and placebo groups over the first four time intervals (i.e., up to the 40th minute).

Other simulated driving measures

The sensitivity of the assay for lane exceedances (number, maximum, and duration) and number of collisions

was established by significantly worse performance in participants administered alprazolam 0.75 mg versus placebo for all measures (all $p < 0.0001$; Table 4). There were no significant differences in all other driving measures for participants administered placebo compared to rapastinel 900 mg or rapastinel 1800 mg (all $p > 0.30$). Ketamine 0.5 mg/kg dosing resulted in significantly worse performance on all measures (all $p < 0.05$). Each of the aforementioned driving measures was significantly improved when comparing rapastinel 900 mg or rapastinel 1800 mg to ketamine 0.5 mg/kg (all $p < 0.03$), except lane exceedance maximums for rapastinel 1800 mg ($p = 0.0862$).

Symbol-digit coding

For the SDC test, the number of correct responses, the proportion of accurate responses, and reaction time were all significantly worse for alprazolam versus placebo (all $p < 0.02$), demonstrating the sensitivity of the test. SDC results for each measure were not significantly different following dosing with rapastinel 900 mg or rapastinel 1800 mg versus placebo (all $p > 0.3$) (Table 5). Following rapastinel 900 mg dosing, SDC results were significantly better than with ketamine 0.5 mg/kg dosing (all $p < 0.04$). Dosing with rapastinel 1800 mg led to significantly greater responses and reaction time (both $p < 0.0001$), but accuracy differences did not reach statistical

TABLE 5 Symbol digit coding results

	RAP 900 mg (*N* = 101)	RAP 1800 mg (*N* = 102)	KET 0.5 mg/kg (*N* = 103)	Alprazolam 0.75 mg (*N* = 100)	Placebo (*N* = 101)	
Number of correct responses						
Mean (SD)	68.42 (8.529)	68.57 (7.811)	62.64 (9.133)	60.76 (9.442)	68.46 (9.856)	
LS means*	68.67	68.63	62.77	61.10	68.55	
Accuracy (%)						
Mean (SD)	99.64 (0.753)	99.60 (0.842)	99.29 (1.379)	99.16 (1.793)	99.51 (1.511)	
LS Means*	99.64	99.61	99.29	99.15	99.54	
SD of reaction time (s)						
Mean (SD)	0.55 (0.197)	0.51 (0.144)	0.60 (0.184)	0.61 (0.277)	0.52 (0.144)	
LS means*	0.54	0.51	0.59	0.61	0.53	
	RAP 900 mg vs. placebo	**RAP 1800 mg vs. placebo**	**RAP 900 mg vs. KET 0.5 mg/kg**	**RAP 1800 mg vs. KET 0.5 mg/kg**	**Alprazolam 0.75 mg vs. placebo**	**KET 0.5 mg/kg vs. placebo**
Number of correct responses						
LSMD (95% CI)*	0.12 (−1.18, 1.42)	0.08 (−1.25, 1.41)	5.90 (4.57, 7.24)	5.87 (4.57, 7.17)	−7.45 (−8.76, −6.15)	−5.79 (−7.13, −4.45)
p value*	0.8609	0.9057	<0.0001	<0.0001	<0.0001	<0.0001
Accuracy (%)						
LSMD (95% CI)*	0.10 (−0.22, 0.43)	0.07 (−0.25, 0.38)	0.35 (0.04, 0.66)	0.32 (−0.00, 0.64)	−0.39 (−0.72, −0.06)	−0.25 (−0.57, 0.07)
p value*	0.5416	0.6639	0.0287	0.0533	0.0195	0.1205
SD of reaction time (s)						
LSMD (95% CI)*	0.01 (−0.03, 0.05)	−0.02 (−0.06, 0.02)	−0.04 (−0.09, −0.00)	−0.08 (−0.11, −0.04)	0.08 (0.04, 0.11)	0.05 (0.01, 0.10)
p value*	0.6233	0.3260	0.0386	<0.0001	<0.0001	0.0139

Note: One participant was excluded from the analyses.

Abbreviations: CI, confidence interval; LSMD, least-squares mean difference; KET, ketamine; RAP, rapastinel.

Number of correct responses = number of items correctly completed in 2 min, high scores reflect better functioning.

Accuracy = percent of items correctly completed, high scores reflect better functioning.

SD of reaction time = variability in reaction time, lower scores indicate better functioning.

*Mixed-effects model with fixed effects for sequence, period, and treatment, with repeated observations based on an unstructured covariance structure, and Kenward-Roger degrees of freedom. The *p* value tests the null hypothesis that the difference in LS means = 0 versus the alternative hypothesis that the difference in LS means ≠ 0. Estimated differences are the first treatment label listed minus the second treatment label.

significance ($p = 0.0533$). Ketamine 0.5 mg/kg intervention compared to placebo resulted in significantly fewer correct responses and increased reaction time (both p values < 0.02), but differences in accuracy were not significant ($p = 0.1205$).

Karolinska sleepiness scale

Participants rated themselves significantly more sleepy following dosing with alprazolam versus placebo (LSMD = 2.3; $p < 0.0001$) (Table 6). Following dosing with rapastinel 900 mg or rapastinel 1800 mg, sleepiness did not differ significantly compared to placebo (LSMD = −0.1; $p = 0.5452$ and LSMD = 0.0; $p = 0.8372$, respectively). Ketamine 0.5 mg/kg significantly increased sleepiness compared to placebo (LSMD = 1.9; $p < 0.0001$). Rapastinel 900 and 1800 mg interventions resulted in less significantly sleepiness compared to ketamine 0.5 mg/kg (900 mg: LSMD = −2.1 and 1800 mg: LSMD = −2.0; both $p < 0.0001$).

TABLE 6 KSS and VAS

	RAP 900 mg ($N = 101$)	RAP 1800 mg ($N = 102$)	KET 0.5 mg/kg ($N = 103$)	Alprazolam 0.75 mg ($N = 100$)	Placebo ($N = 101$)
KSS					
Mean (SD)	3.1 (1.66)	3.3 (1.67)	5.2 (1.87)	5.6 (1.95)	3.3 (1.76)
LS Means*	3.2	3.3	5.2	5.6	3.3
VAS motivation					
Mean (SD)	64.6 (29.21)	67.9 (25.53)	52.3 (31.04)	38.7 (32.27)	69.2 (26.61)
LS means*	64.4	68.0	52.2	37.9	69.2
VAS self-appraisal of driving performance					
Mean (SD)	68.5 (25.83)	66.8 (25.60)	57.5 (30.35)	25.8 (27.22)	70.1 (24.90)
LS means*	67.2	67.2	58.2	24.2	69.3
	RAP 900 mg vs. placebo	**RAP 1800 mg vs. placebo**	**RAP 900 mg vs. KET 0.5 mg/kg**	**RAP 1800 mg vs. KET 0.5 mg/kg**	**Alprazolam 0.75 mg vs. placebo**
KSS					
Difference in LS means*					
p value*	0.5234	0.8116	<0.0001	<0.0001	<0.0001
VAS motivation					
Difference in LS means*	−4.9	−1.3	12.2	15.8	−31.4
p value*	0.1021	0.6778	<0.0001	<0.0001	<0.0001
VAS self-appraisal of driving performance					
Difference in LS means*	−2.1	−2.1	9.0	9.0	−45.1
p value*	0.5040	0.4836	0.0034	0.0038	<0.0001

Note: One participant was excluded from the analyses.

Abbreviations: CI, confidence interval; LS, least squares KET, ketamine; KSS, Karolinska Sleepiness Scale; LS, least squares; RAP, rapastinel; VAS, visual analog scale.

The KSS is a self-report measure of sleepiness based on a 9-point categorical Likert scale: (1) extremely alert, (2), (3) alert, (4), (5) neither sleepy nor alert, (6), (7) sleepy—but no difficulty remaining awake, and (8), (9) extremely sleepy—fighting sleep.

VAS – Motivation is based on a 100-mm horizontal, linear visual analog scale from not motivated (0) to motivated (100), in response to the question: How motivated did you feel to drive at your best during the last 60 minutes of driving?

VAS – Self-appraisal of driving performance results were based on a 100-mm horizontal, linear visual analog scale from not satisfactory (0) to satisfactory (100), in response to the question: How well you think you drove for the last 60 minutes?

*Mixed-effects model with fixed effects for sequence, period, and intervention, with repeated observations based on an unstructured covariance structure, and Kenward-Roger degrees of freedom. The *p* value tests the null hypothesis that the difference in LS means = 0 versus the alternative hypothesis that the difference in LS means ≠ 0. Estimated differences are the first intervention label minus the second intervention label (e.g., difference in LS means for Rapastinel 900 mg vs. placebo reflects Rapastinel 900 mg LS mean minus placebo LS mean).

Subjective assessments

Following dosing with alprazolam 0.75 mg, participants self-rated their motivation and driving performance significantly below placebo ($p < 0.0001$ and $p = 0.0003$; Table 6) and fewer participants rated themselves ready to drive compared to placebo ($p < 0.0001$). No significant differences in self-rated readiness to drive, motivation to drive, or driving performance were observed for either rapastinel dose compared to placebo (all p values >0.10). Ketamine participants self-rated themselves worse than placebo participants (all $p < 0.0004$) for each measure. Compared to the ketamine 0.5 mg/kg dosing group, both rapastinel dosing groups reported significantly higher levels of self-reported motivation and driving performance (both $p < 0.004$). Greater proportions of participants rated themselves ready to drive after dosing with rapastinel 900 mg (98.0%) and rapastinel 1800 mg (97.9%) compared to ketamine 0.5 mg/kg (75.0%) and alprazolam (79.6%).

Safety

Treatment-emergent AEs (TEAEs) were reported in the greatest number of participants following ketamine (98.1%) and alprazolam (97.0%) treatments, whereas the rapastinel and placebo groups had similar rates of TEAEs (~ 46%). The most common TEAEs in both rapastinel groups were headache and somnolence. Dizziness, euphoric mood, and nausea were the most common TEAEs in ketamine participants. In the alprazolam group, somnolence and dizziness were the most commonly reported TEAEs. No deaths or SAEs were reported.

Most AEs were mild to moderate in severity for all interventions. SAEs were experienced in three participants (2.9%) within the ketamine intervention (1 incidence of each: vision blurred, syncope, anxiety, euphoric mood, and dyspnea; all considered related to treatment), two participants (2.0%) within the rapastinel 1800 mg intervention (diarrhea [not related], syncope [related]), and one participant (1.0%) in the rapastinel 900 mg (blood creatine phosphokinase increased and transaminases increased, both not related) and alprazolam (somnolence [related]) interventions. No clinically significant laboratory, vital sign, ECG, or C-SSRS findings occurred during the study.

DISCUSSION

The CRCDS-MiniSim driving simulation test has been validated in numerous studies assessing the effects of drugs on driving performance.[19,29–31] Study sensitivity of all assays (driving and cognitive performance, subjective assessments, and sleepiness) was established with alprazolam, which was consistently significantly worse than placebo in each measure (all $p < 0.05$). To our knowledge, this is the first study investigating the effects of rapastinel on driving performance.

This study found that rapastinel does not impact simulated driving performance. Both rapastinel doses were similar to placebo in simulated driving performance (SDLP and all other driving performance measures) and each upper limit of the 95% CI did not exceed the prespecified noninferiority margin, which is based on a BAC of 0.05% that is known to impair driving.[27] Consistent with these findings, both rapastinel doses did not appreciably impact cognitive ability, self-perceived safety and performance, and sleepiness compared to placebo. Ad hoc analysis results indicated that participants maintained an SDLP similar to placebo throughout the 60-min driving simulation. A slight, nonsignificant increase occurred for placebo and both rapastinel doses throughout the task, but this is likely attributable to task-related fatigue secondary to the monotonous nature of the driving task.

Ketamine significantly impaired simulated driving performance and all related domains assessed in this first large placebo-controlled, randomized, cross-over simulated driving study of this drug. The mean difference in SDLP between ketamine and placebo was +4.08 cm, exceeding the upper limit of the 95% CI of both rapastinel groups; the 95% CI for ketamine (+6.14 cm) exceeded the noninferiority margin (+4.4 cm) indicating a greater impact of ketamine on driving than a BAC of 0.05%. Driving results presented herein are similar to what has been shown in a smaller ($N = 20$) open-label driving simulator study comprising a younger and predominantly male population,[15] providing further evidence that ketamine has deleterious effects on driving.

The effects of rapastinel on simulated driving performance were also compared to ketamine. Ketamine compromised driving ability for a minimum of 105 min after dosing, and significantly impaired driving performance, cognitive ability, self-assessed safety and performance, and sleepiness compared to either rapastinel dose. These findings could be significant to researchers and clinicians because it shows that impairment of driving ability does not occur across the entire class of NMDAR modulators, a promising drug class of medication for patients with treatment-resistant MDD. Previous studies have shown the positive allosteric modulatory action of rapastinel does not induce dissociation or psychomimetic effects.[11] This difference between rapastinel and ketamine may explain ketamine's significant impairing effect on driving.

Safety profiles for rapastinel, alprazolam, and ketamine were consistent with those previously reported;

no new safety signals were identified. TEAEs occurred in nearly every participant following ketamine dosing and 97% of alprazolam participants. Conversely, less than half of participants reported TEAEs after treatment with either rapastinel dose or placebo. Overall, the most common TEAEs for all treatments combined were somnolence, dizziness, headache, nausea, and euphoric mood.

Study limitations include a potential unblinding of participants in the ketamine group due to its known dissociative and sedative effects. Healthy, young participants with no suicidal ideation, sleep disturbances, or signs/symptoms of MDD were chosen to avoid potential effects of disease- or symptom-related factors. Investigating the effects of these medications on patients with MDD would be an appropriate next step. An additional limitation is that the study was not powered to detect significant treatment differences on secondary additional end points.

ACKNOWLEDGEMENTS

The authors would like to thank the participants who participated in this trial and the investigators and study staff at the individual sites. Writing assistance and editorial support in the preparation of this manuscript was provided by Cherisse Loucks, PhD, of AbbVie Inc. (Madison, New Jersey).

CONFLICT OF INTEREST

R.B. is a full-time employee at AbbVie, Inc. (previously Allergan plc). S.S., J.R., C.S., and A.P. are former full-time employees at AbbVie, Inc. (previously Allergan plc). T.H. (Chief Executive Officer, Owner) and G.K. (President, Chief Scientific Officer, Owner) of Cognitive Research Corporation and G.K. (Author, Owner) of CogScreen.

AUTHOR CONTRIBUTIONS

S.S., G.K., T.H., J.R., J.C.R., R.B., and A.P. wrote the manuscript. S.S., G.K., T.H., J.R., J.C.R., R.B., and A.P. designed the research. G.K. and T.H. performed the research. All authors analyzed the data. G.K. and T.H. contributed new reagents/analytical tools.

REFERENCES

1. Friedrich MJ. Depression is the leading cause of disability around the world. *JAMA*. 2017;317:1517.
2. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*. 2018;75:336-346.
3. Greenberg PE, Fournier AA, Sisitsky T, Pike CT, Kessler RC. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry*. 2015;76:155-162.
4. Warden D, Rush AJ, Trivedi MH, Fava M, Wisniewski SR. The STAR*D Project results: a comprehensive review of findings. *Cur Psychiatr Rep*. 2007;9:449-459.
5. IsHak WW, Mirocha J, James D, et al. Quality of life in major depressive disorder before/after multiple steps of treatment and one-year follow-up. *Acta Psychiatr Scand*. 2015;131:51-60.
6. Ionescu DF, Papakostas GI. Experimental medication treatment approaches for depression. *Transl Psychiatry*. 2017;7:e1068.
7. Posternak MA, Zimmerman M. Is there a delay in the antidepressant effect? A meta-analysis. *J Clin Psychiatry*. 2005;66:148-158.
8. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry*. 2003;53:649-659.
9. Iadarola ND, Niciu MJ, Richards EM, et al. Ketamine and other N-methyl-D-aspartate receptor antagonists in the treatment of depression: a perspective review. *Ther Adv Chronic Dis*. 2015;6:97-114.
10. Abdallah CG, Sanacora G, Duman RS, Krystal JH. Ketamine and rapid-acting antidepressants: a window into a new neurobiology for mood disorder therapeutics. *Ann Rev Med*. 2015;66:509-523.
11. Moskal JR, Burch R, Burgdorf JS, et al. GLYX-13, an NMDA receptor glycine site functional partial agonist enhances cognition and produces antidepressant effects without the psychotomimetic side effects of NMDA receptor antagonists. *Expert Opin Investig Drugs*. 2014;23:243-254.
12. Moskal JR, Burgdorf J, Stanton P, et al. The development of rapastinel (formerly GLYX-13); a rapid acting and long lasting antidepressant. *Cur Neuropharmacol*. 2016;14:1-9.
13. Giorgetti R, Marcotulli D, Tagliabracci A, Schifano F. Effects of ketamine on psychomotor, sensory and cognitive functions relevant for driving ability. *Forensic Sci Int*. 2015;252:127-142.
14. van de Loo AJAE, Bervoets AC, Mooren L, et al. The effects of intranasal esketamine (84 mg) and oral mirtazapine (30 mg) on on-road driving performance: a double-blind, placebo-controlled study. *Psychopharmacology*. 2017;234:3175-3183.
15. Hayley AC, Green M, Downey LA, et al. The acute and residual effects of escalating, analgesic-range doses of ketamine on driving performance: a simulator study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2018;86:83-88.
16. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. *Sleep*. 1991;14:540-545.
17. Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry*. 2011;168:1266-1277.
18. Jaeger J. Digit symbol substitution test: the case for sensitivity over specificity in neuropsychological testing. *J Clin Psychopharmacol*. 2018;38:513-519.
19. Kay GG, Horohonich S, Hochadel TJ. CRCDS-MiniSim: a standardized test for drug impaired driving. ASCP 2018 Annual Meeting (Poster) (2018).
20. XANAX (alprazolam tablet) Prescribing Information (Pharmacia and Upjohn Company, New York, NY, 2021).
21. Sinner B, Graf BM. Ketamine. In: Schüttler J, Schwilden H, eds. *Modern Anesthetics. Handbook of Experimental Pharmacology*. Springer; 2008: 313-333.
22. Preskorn S, Macaluso M, Mehra DV, et al. Randomized proof of concept trial of GLYX-13, an N-methyl-D-aspartate receptor glycine site partial agonist, in major depressive disorder nonresponsive to a previous antidepressant agent. *J Psychiatric Pract*. 2015;21:140-149.

23. United States Food and Drug Administration. Evaluating drug effects on the ability to operate a motor vehicle guidance for industry (2017).
24. Verster JC, Volkerts ER, Verbaten MN. Effects of alprazolam on driving ability, memory functioning and psychomotor performance: a randomized, placebo-controlled study. *Neuropsychopharmacology*. 2002;27:260-269.
25. Verster JC, Volkerts ER. Clinical pharmacology, clinical efficacy, and behavioral toxicity of alprazolam: a review of the literature. *CNS Drug Rev*. 2004;10:45-76.
26. Murrough JW, Iosifescu DV, Chang LC, et al. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. *Am J Psychiatry*. 2013;170:1134-1142.
27. Louwerens JW, Gloerich ABM, De Vries G, Brookhuis KA, O'Hanlon JF. The relationship between drivers' blood alcohol concentration (BAC) and actual driving performance during high speed travel. In: Noordzij PC, Roszbach R, eds. *Alcohol, Drugs and Traffic Safety-T86*. Excerpta Medica; 1987:183-186.
28. Kaida K, Takahashi M, Åkerstedt T, et al. Validation of the Karolinska sleepiness scale against performance and EEG variables. *Clin Neurophysiol*. 2006;117:1574-1581.
29. Simen A, Gargano C, Cha J-H, et al. A randomized, crossover, placebo-controlled clinical trial to assess the sensitivity of the CRCDS Mini-Sim to the next-day residual effects of zopiclone. *Ther Adv Drug Saf*. 2015;6:86-87.
30. Kay GG, Schwartz HI, Wingertzahn MA, Jayawardena S, Rosenberg RP. Next-day residual effects of gabapentin, diphenhydramine, and triazolam on simulated driving performance in healthy volunteers: a phase 3, randomized, double-blind, placebo-controlled, crossover trial. *Hum Psychopharmacol*. 2016;31:217-226.
31. Sun H, MacLeod C, Mostoller K, et al. Early-stage comparative effectiveness: randomized controlled trial with histamine inverse agonist MK-7288 in excessive daytime sleepiness patients. *J Clin Pharmacol*. 2013;53:1294-1302.

How to cite this article: Su S, Kay G, Hochadel T, et al. A randomized, multicenter trial assessing the effects of rapastinel compared to ketamine, alprazolam, and placebo on simulated driving performance. *Clin Transl Sci*. 2022;15:255–266. https://doi.org/10.1111/cts.13145