

PHASE I, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSSOVER STUDY TO COMPARE THE PHARMACOKINETICS OF A SINGLE ORAL DOSE OF A NEW ZALEPLON FORMULATION (SKP-1041) AND OPEN-LABEL ZALEPLON IN HEALTHY ELDERLY SUBJECTS

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INTRODUCTION

Insomnia symptoms increase with age, especially problems with sleep maintenance. A novel formulation of zaleplon (SKP-1041) that releases active drug via proprietary Geoclock[®] technology provides an extended plasma concentration profile compared to commercially-available zaleplon 10 mg (Sonata[®]). This study compared the pharmacokinetics of a single oral dose of SKP-1041 15 mg and commercially-available zaleplon 10 mg (ZAL), and next-morning neurobehavioral effects when administered to healthy elderly subjects.

OBJECTIVES

Primary: To compare the plasma pharmacokinetic profile of a single oral dose of SKP-1041 (15 mg) to ZAL (10 mg) when administered at night to healthy elderly subjects.

Secondary: To assess next-day residual effects including alertness, subjective sleepiness, effect on immediate and working memory, effect on memory consolidation; safety and tolerability.

TREATMENT

- SKP-1041 is a new formulation of zaleplon, a non-benzodiazepine hypnotic agent, which utilizes SkyePharma PLC's (LSE: SKP) proprietary Geoclock[®] technology for delayed release. Active drug in SKP-1041 is zaleplon 15 mg, formulated to release 2 hours after ingestion followed by a 2-hour controlled release of zaleplon.
- ZAL is commercially-available immediate-release zaleplon 10 mg.
- Matching placebo

METHODS

Single-center, double-blind, randomized, three-way crossover study with three treatment periods of two nights each in which elderly subjects randomly received SKP-1041, ZAL, or placebo.

- Inclusions: ≥ 65 years of age; good general health; body mass index 18 – 32 kg/m²; 12-lead ECG within normal range; usual bedtime between 10:00 PM and 1:00 AM; valid driving license for 2 years.
- Exclusions: Foreseeable need for medical treatment during the study period; presence of a sleep disorder or disturbed sleep/wake patterns; recent bereavement; use of prescription or over-the-counter medication (except acetaminophen) within 14 days of study admission; use of treatments with CNS effects within 1 month of study admission; consumption of >40 g of alcohol/day; >10 cigarettes or equivalent /day; consumption of >500 mg/day of caffeine; need for a nap after a meal; history of repeated falls/fractures within the past 2 years.
- All participants signed an informed consent and the study was conducted in compliance with good clinical practice and the Declaration of Helsinki (1964).

Study procedures

- Subjects randomly received an oral dose of SKP-1041 15 mg, ZAL 10 mg, or placebo at approximately 10:30 PM on Day 1 and Day 2 of each of three treatment periods. SKP-1041 and placebo were administered in a double-blind manner; administration of ZAL was open-label.
- Subjects remained in the laboratory from Day -1 to Day 3; minimum 4-day washout between periods.

Pharmacokinetic evaluation

- Blood was drawn on Day 2 of each condition predose, and postdose at 1 and 2 hrs, every ½ hour through 8 hrs postdose, then every hour through 12 hrs postdose (20 samples per profile).

Pharmacodynamic evaluations

- Subjects had a training session for the digit symbol substitution test (DSST), the psychomotor vigilance test (PVT), and the paired-associate wordlist task (PAWT) on Day -1.
- Driving simulation was conducted on Day 1 and within 2 hours of awakening on Day 2. The PVT, DSST, digit span test (DST) and Karolinska Sleepiness Scale (KSS) were assessed on Day 1 prior to dosing (baseline) and on Day 2 within the first hour of awakening.
- PAWT was assessed on Day 1 at approximately 8:00 PM and on Day 2 one hour after awakening.

RESULTS

Twenty-four subjects were randomized; 23 subjects received at least one dose of investigational drug and were evaluated for safety (one subject was not compliant for driving simulation and did not receive drug). Twenty-two subjects (13 males, 9 females; ages 65 – 73) were evaluated for pharmacokinetics and pharmacodynamics; one subject discontinued due to non-compliance with protocol.

Pharmacokinetics

- Figure 1 displays mean plasma concentrations for SKP-1041 and ZAL. Median T_{max} for SKP-1041 (3.75 hr; range: 2 – 5.5 hr) and ZAL (2.0 hr; range: 1 – 4 hr) was significantly different ($p < 0.001$). Mean (\pm SE) C_{max} (ng/mL) for SKP-1041 and ZAL was 25.5 ± 2.4 and 15.8 ± 1.6 , respectively. Drug exposure (total AUC) was greater with SKP-1041 (74.6 ± 7.2 ng·h/mL) compared to ZAL (50.3 ± 4.8 ng·h/mL); differences in C_{max} and AUC were attributable to dosage differences. $T_{1/2}$ was similar between SKP-1041 (1.42 ± 0.04 hr) and ZAL (1.47 ± 0.06 hr).
- Kinetic profiles resembled those reported for young subjects.¹ There was no evidence of impaired clearance of zaleplon in the elderly subjects.

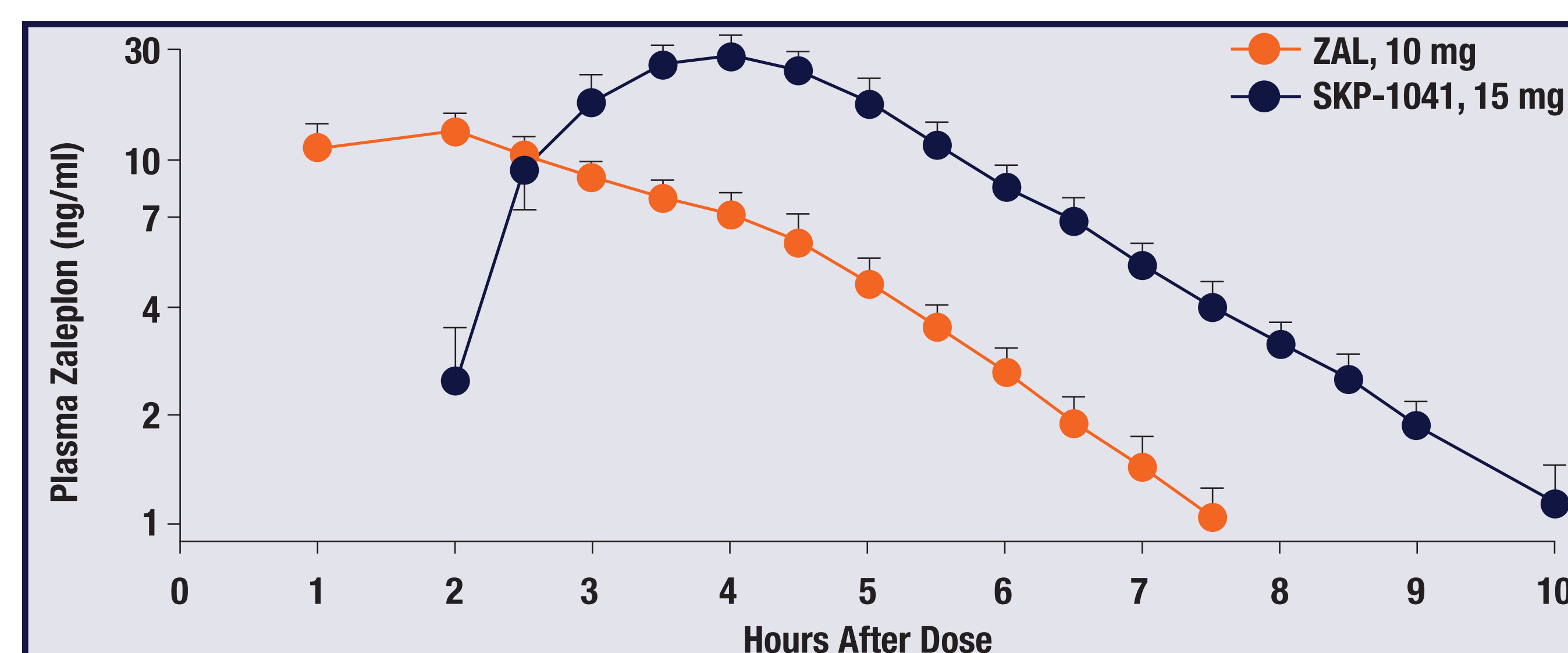


Figure 1. Mean (\pm SE) plasma zaleplon concentrations.

Pharmacodynamic evaluations

- Pharmacodynamic assessments of neurobehavioral functions showed no impairment or residual effects with SKP-1041 compared with placebo as illustrated in Figures 2 – 6. Importantly, there were no differences observed for alertness (driving simulation), psychomotor speed and vigilance (PVT), psychomotor speed and attention (DSST), short term and working memory (DST), subjective sleepiness (KSS), or memory consolidation (PAWT; data not shown).

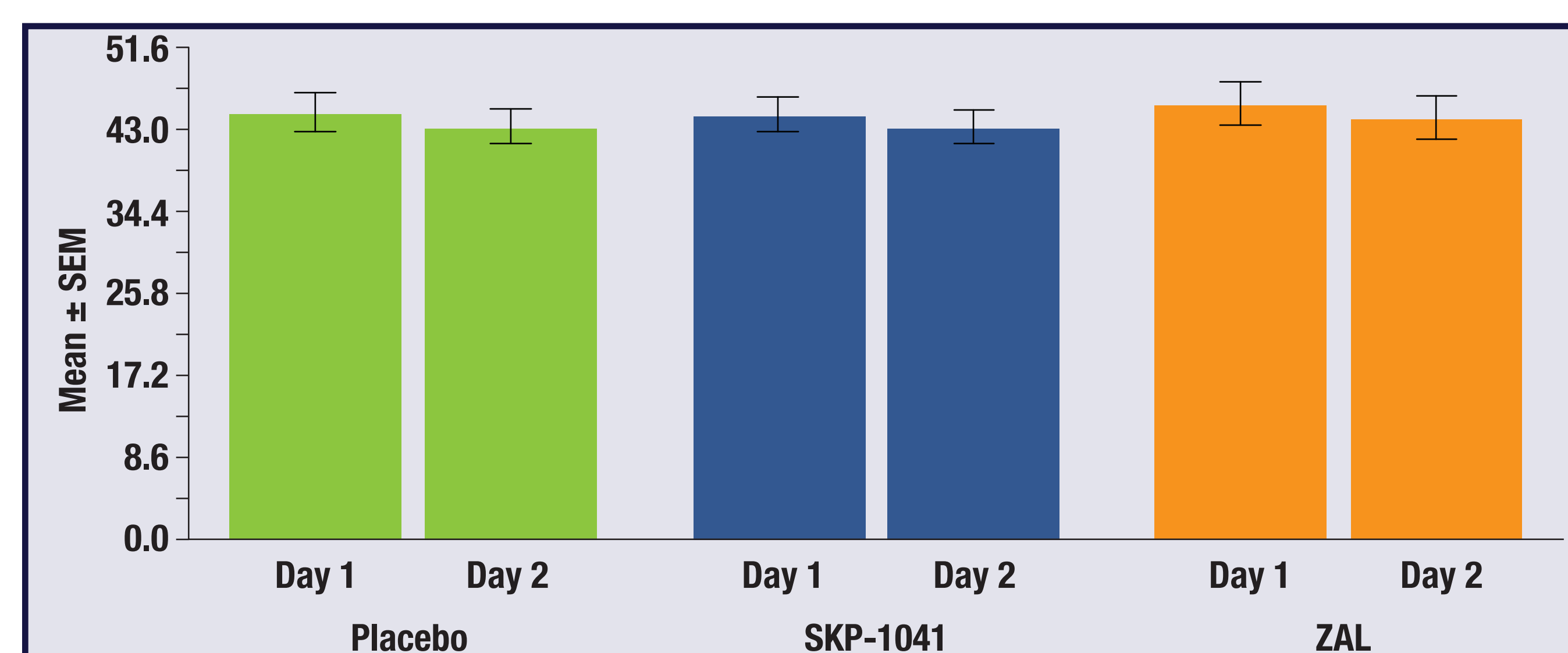


Figure 2. Results of driving simulation for each study condition. Mean \pm SEM of standard deviation of lateral position (cm) recorded predose on Day 1 and postdose on Day 2 during the second hour after awakening. Test duration was 1 hour. No significant differences were noted between treatments or between pre- and postdose evaluations.

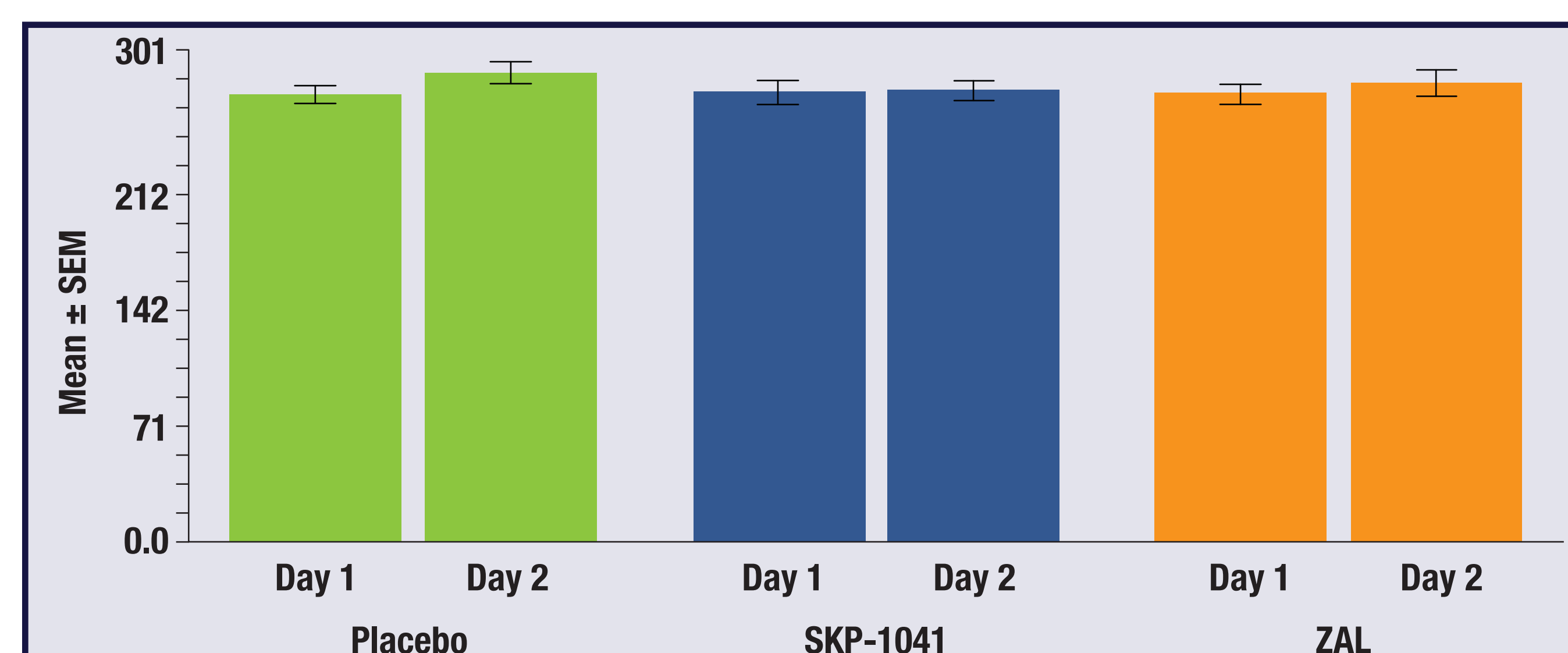


Figure 3. Mean reaction time for the psychomotor vigilance test (PVT) by treatment and study day. No significant differences were noted between treatments or study days.

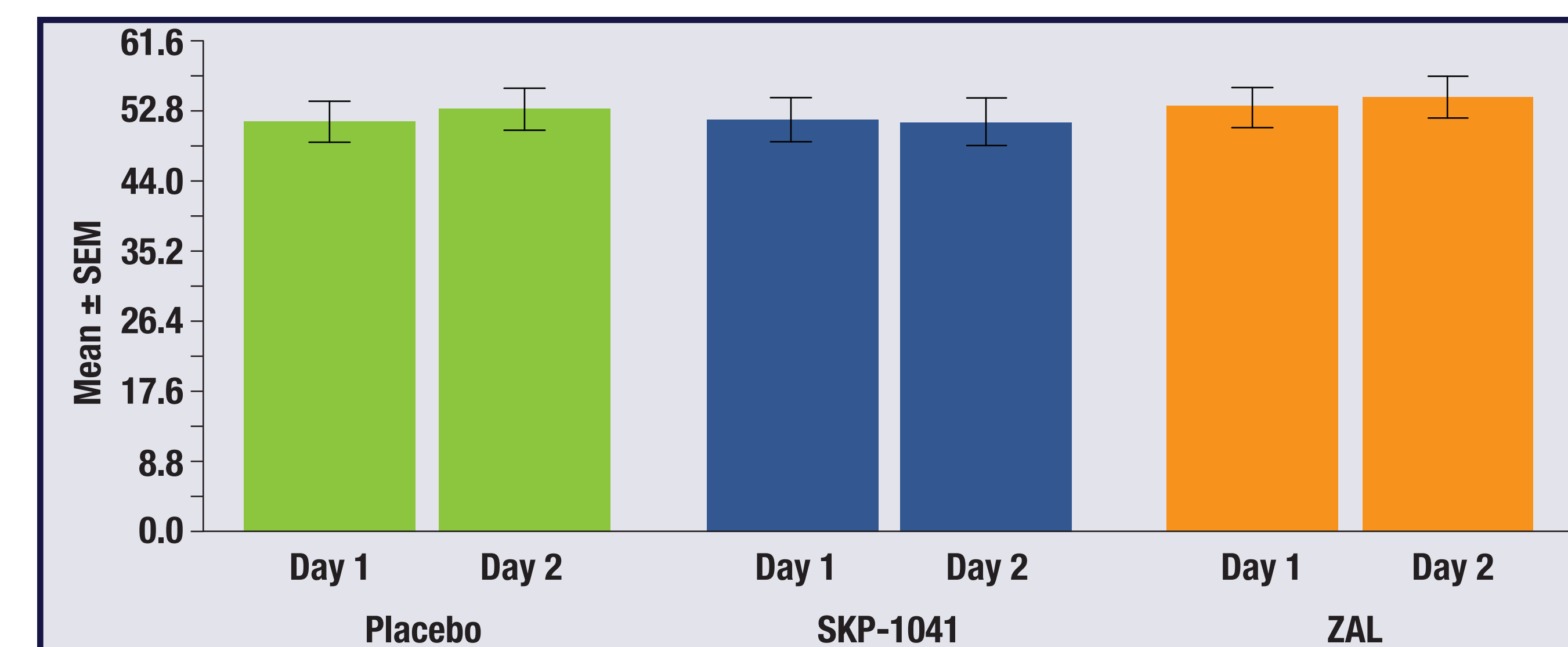


Figure 4. Mean number of correct answers for the digit symbol substitution test (DSST) by treatment and study day. No significant differences were noted between treatments or study days.

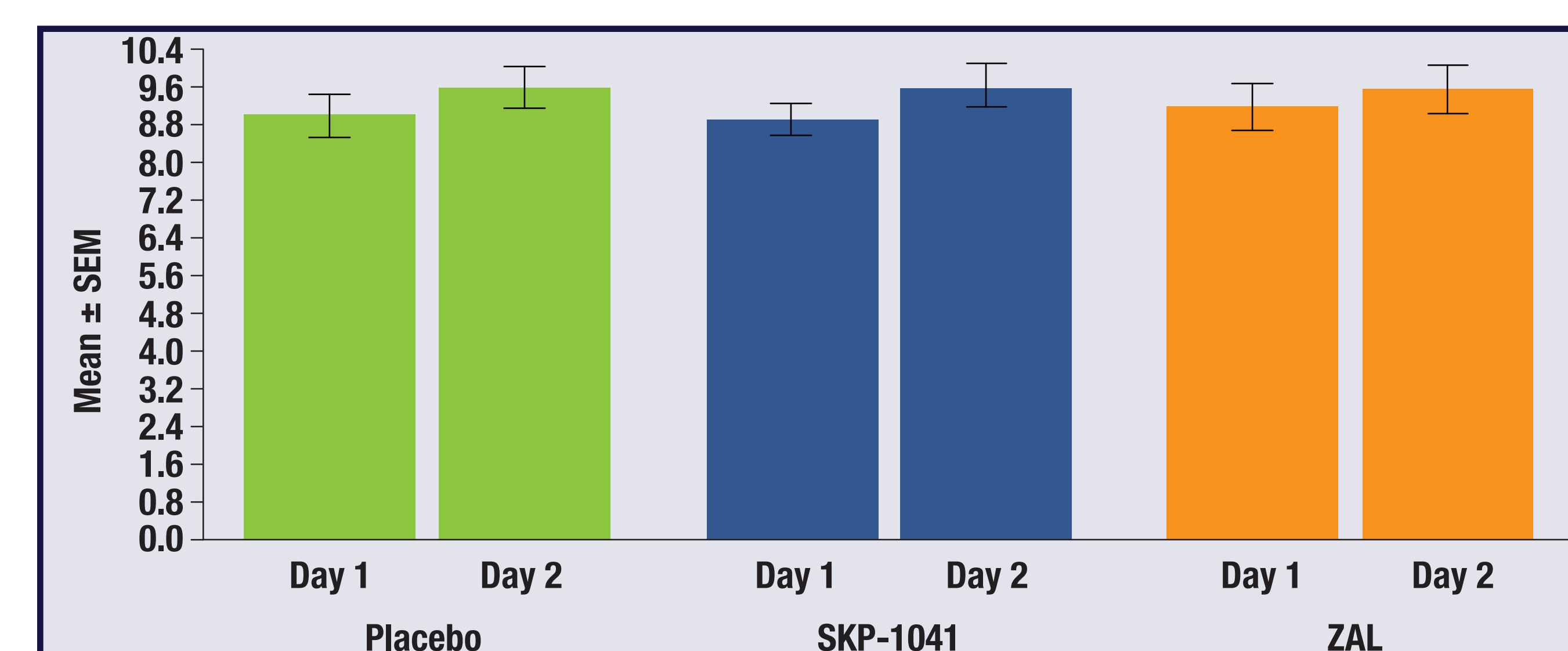


Figure 5. Mean direct total score for the digit span test (DST) by treatment and study day. No significant differences were noted between treatments or study days.

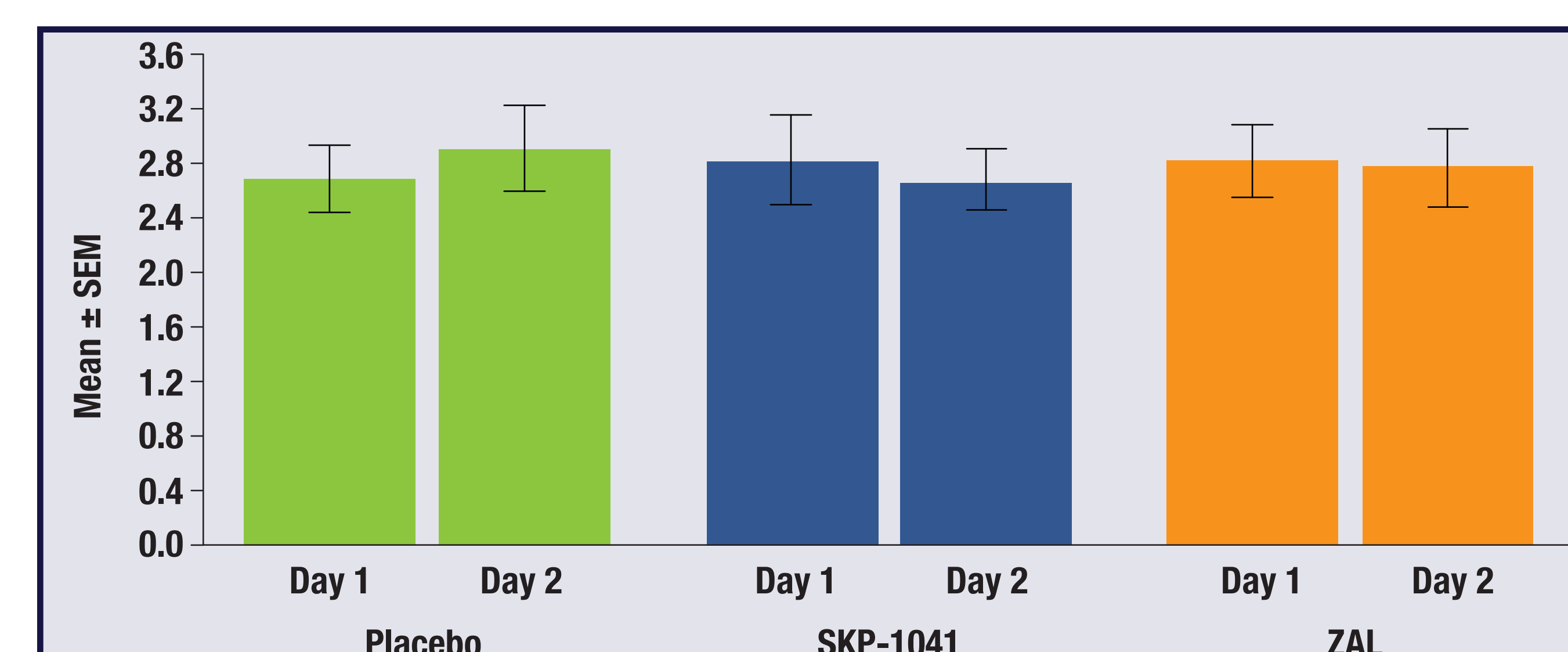


Figure 6. Mean sleepiness scores for the Karolinska Sleepiness Scale (KSS) by treatment and study day. No significant differences were noted between treatments or study days.

Safety

- SKP-1041 was well-tolerated, with 8 adverse events (AEs) reported in 7 subjects. Seven AEs were treatment-emergent (3 placebo; 3 SKP-1041; 1 ZAL) with two considered treatment-related after placebo (severe somnolence) and SKP-1041 (moderate middle-of-the-night insomnia).

CONCLUSIONS

- The pharmacokinetic profile and AUC of SKP-1041 15 mg in these elderly subjects were consistent with previous results in young subjects.
- There were no next-morning neurobehavioral effects or cognitive impairment with SKP-1041.
- SKP-1041 15 mg was well-tolerated in the elderly.

REFERENCES

- Gassen, et al. Pharmacokinetic Profile of Single Oral Doses of Zaleplon in Three Novel Release Formulations in Normal Volunteers. SLEEP 2009;32:A267 (abstract 0817).

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