

PHASE I, RANDOMIZED, CROSSOVER STUDY TO COMPARE DAY VS NIGHT PHARMACOKINETICS OF A SINGLE ORAL DOSE OF A NEW ZALEPLON FORMULATION IN HEALTHY YOUNG VOLUNTEERS

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INTRODUCTION

The majority of insomnia patients report difficulty with sleep maintenance and there is a significant unmet need for an adequate therapeutic option. Ideal treatment for middle-of-the-night awakening would provide an effective hypnotic when needed without interfering with normal sleep architecture or next-day cognitive function. SKP-1041 is a novel formulation of zaleplon that releases active drug via proprietary Geoclock[®] technology. SKP-1041 has been shown to have a pharmacokinetic profile consistent with drug release during the middle hours of the night. By delaying drug release, there is no interference with natural sleep induction and slow-wave sleep. Because zaleplon has a very short 1-hour half-life, there is reduced chance for next-day residual drug effects.

A previous phase I study was conducted that evaluated the pharmacokinetics of SKP-1041 in healthy volunteers.¹ In that study subjects received SKP-1041 in a laboratory setting during daylight hours. The following study expands these findings to nighttime administration, and examines proof-of-concept for effective sleep maintenance.

OBJECTIVES

Primary objective: To determine if there is a difference in the pharmacokinetic profile of a single 15-mg oral dose of SKP-1041 with daytime and nighttime dosing.

Secondary objectives: To assess the effect of SKP-1041 15 mg on wake after sleep onset (WASO) using polysomnography (PSG) in a noise-induced transient insomnia model, and to evaluate 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.

METHODS

Single-center randomized, open-label, two-way crossover study in healthy young volunteers.

- Inclusions: 20 – 50 years of age; good general health; body mass index 18 – 30 kg/m²; females practicing effective birth control, surgically sterile, or ≥12 months postmenopausal.
- Exclusions: Presence of a sleep disorder or disturbed sleep/wake patterns; use of prescription or over-the-counter medication (except acetaminophen) within 14 days of study admission; consumption of >40 g of alcohol/day; >10 cigarettes or equivalent/day; consumption of >500 mg/day of caffeine.
- All participants signed an informed consent and the study was conducted in compliance with good clinical practice and the Declaration of Helsinki (1964).

Pharmacokinetic evaluation for time-of-day effects

- Subjects were randomized to receive SKP-1041 at 9:00 AM or 10:30 PM during two 1-day study periods in counterbalanced fashion, separated by a 4-day washout.
- In each period blood was drawn -2h and -1h predose; postdose at 1h, 2h, every 30min through 9h, then hourly through 12h (20 blood draws).

SKP-1041 effect on arousal and WASO

- During a third two-night study period, subjects received in random and counterbalanced order, either SKP-1041 or matching placebo at 10:30 AM with a 1-day washout between study nights.

- PSG arousals (defined according to American Academy of Sleep Medicine [AASM] 2007 criteria) and WASO were measured during four 30-minute noise periods during which subjects were exposed to car and truck noise at 1:00, 2:30, 4:00, and 5:30 AM, with decibels (dB) increasing from 40 to 55 dB (Figure 1). For each noise period the percentage of noise producing an arousal in the 60 seconds following a noise exposure was calculated.

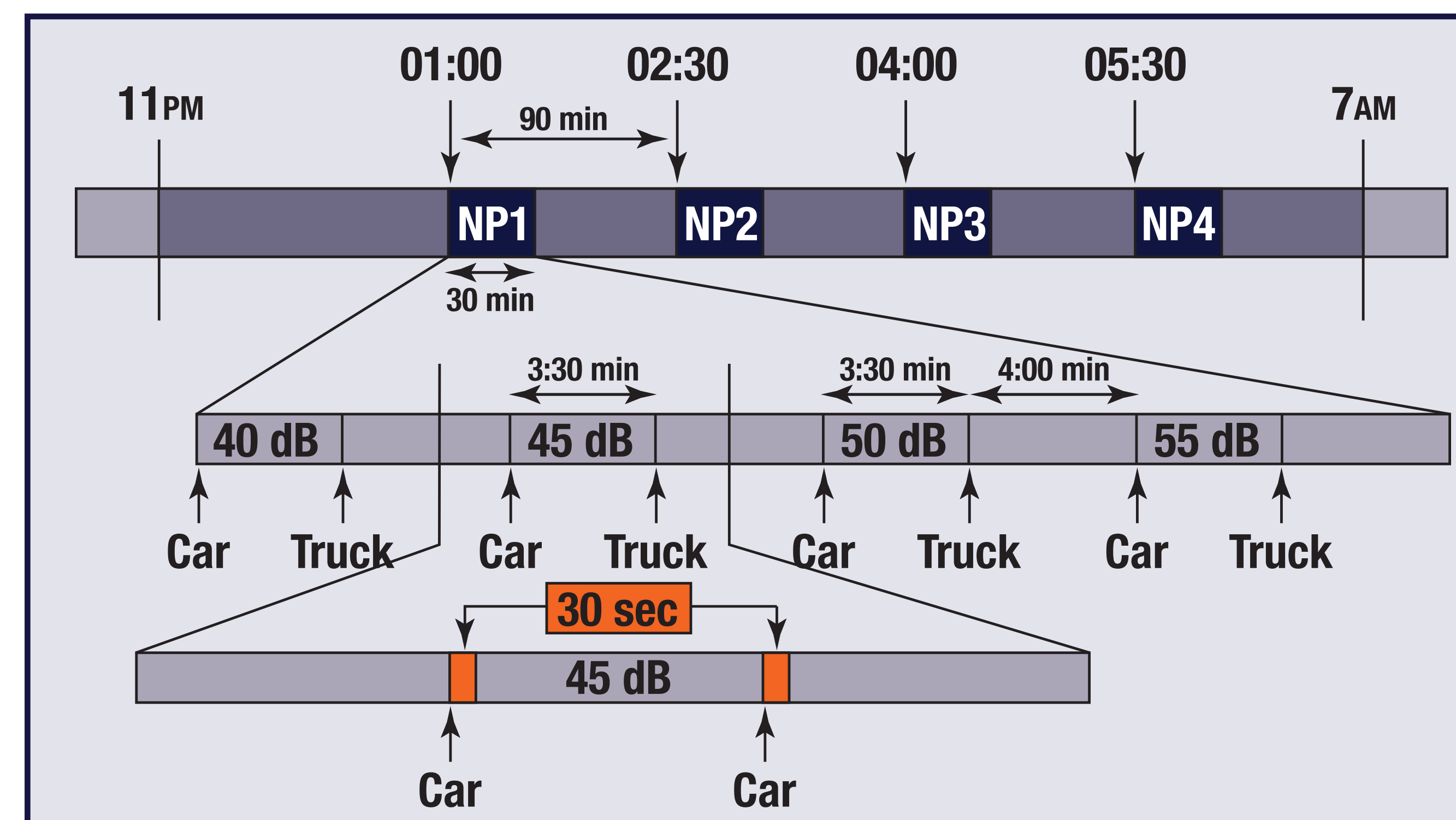


Figure 1. Noise-induced insomnia model.

Safety assessments

- Physical examinations, vital signs, and tracking of adverse events were performed during baseline, all treatment periods, and on the final study day. At screening and end-of-study, subjects had a 12-lead ECG and clinical laboratory tests (chemistry, hematology, urinalysis).

RESULTS

Of 25 eligible subjects, 24 were randomized and 23 (8 males, 15 females; ages 20 – 46) completed and were evaluated. Due to technical problems, PSG data were available for 21 and 22 subjects during treatment with active drug and placebo, respectively.

Day versus night pharmacokinetics

- Figure 2 shows zaleplon concentrations following day and night administration of SKP-1041.
- Net systemic exposure to zaleplon was statistically indistinguishable between day and night administrations of SKP-1041. Zaleplon plasma AUCs were similar after both day (84.6 ± 8.7 ng·h/mL) and night (85.4 ± 10.2 ng·h/mL) administration.
- For both day and night dosing, zaleplon C_{max} occurred at a median of 3.5 to 4.0 hrs postdose.

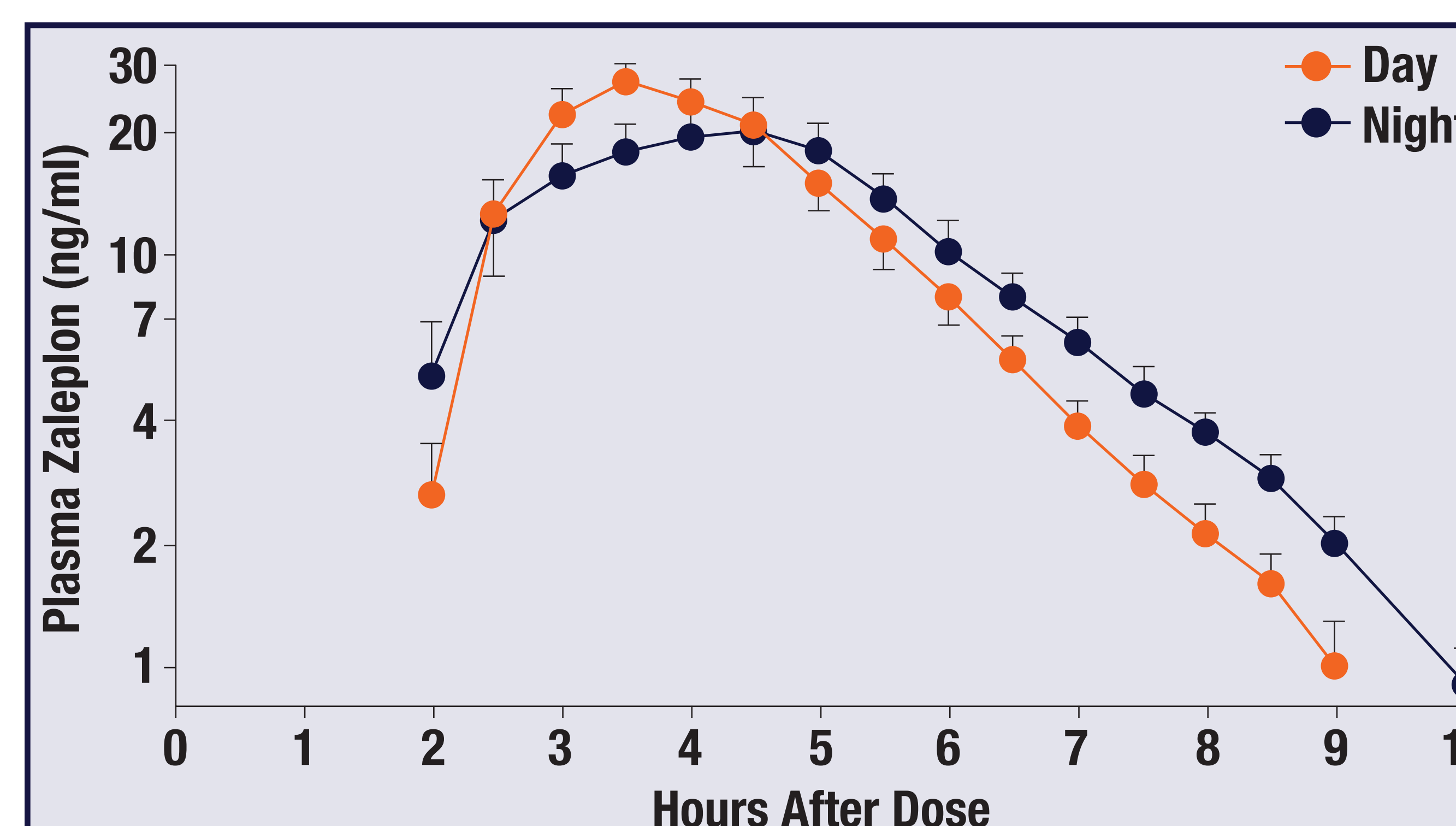


Figure 2. Mean plasma zaleplon concentrations after day and night administration of SKP-1041. Logarithmic concentration axis.

SKP-1041 effect on WASO

- During noise period 2 (2:30 AM) at zaleplon C_{max}, subjects on SKP-1041 had significantly (p<0.05) fewer arousals in the 60 seconds following noise exposure (Figure 3) and spent significantly (p<0.05) less time awake (Figure 4).

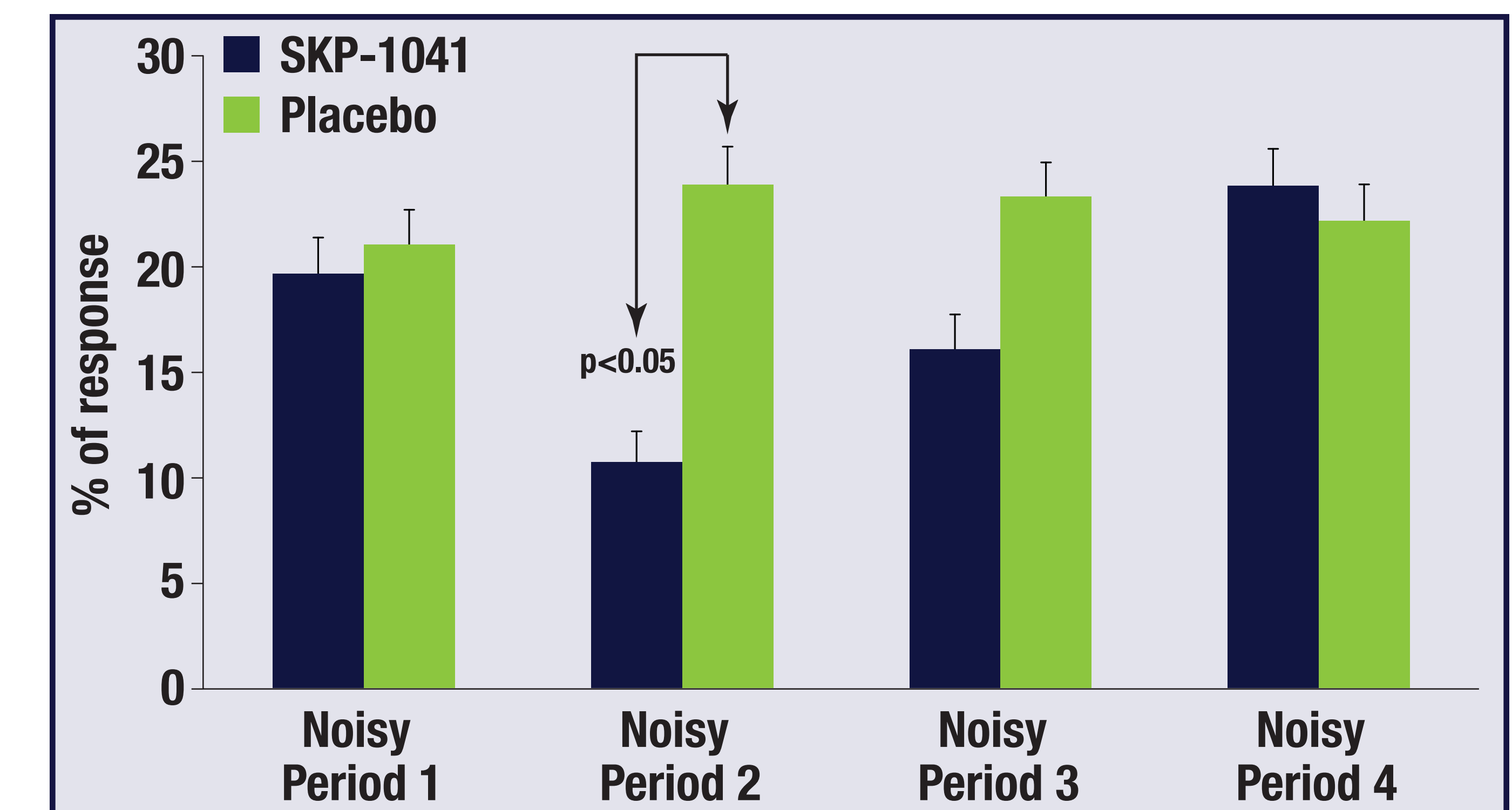


Figure 3. Comparison of the effects of SKP-1041 and placebo on the percentage of AASM-defined arousal following the 8 noise presentations in the noise periods.

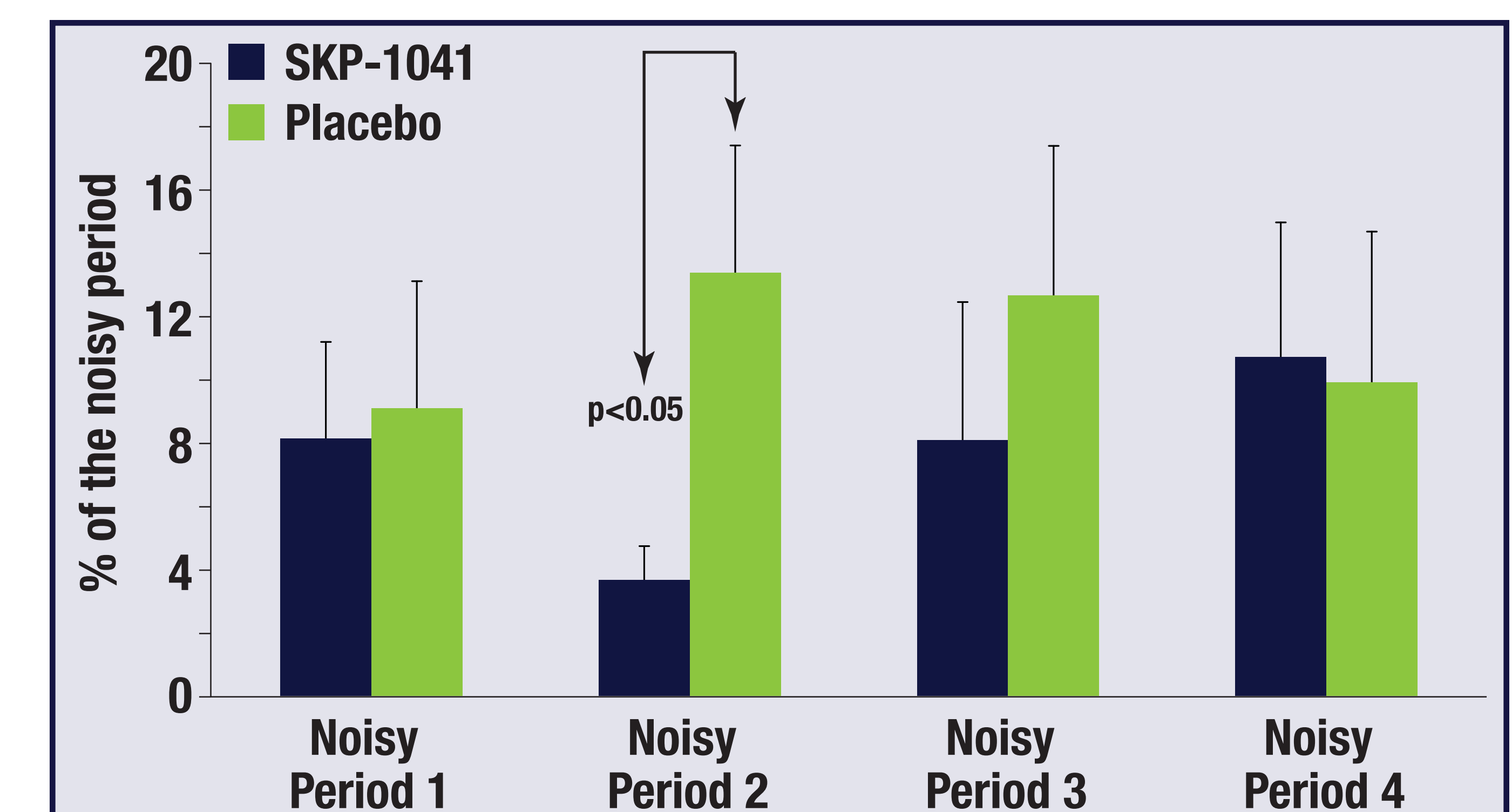


Figure 4. Comparison of the effects of SKP-1041 and placebo on percentage of WASO during each of the four 30-minute noise periods.

Safety

- SKP-1041 was well-tolerated in all (N=24) subjects.
- No serious adverse events were reported. The most frequent treatment-emergent adverse event was headache (4 events) in three subjects, one of which was considered treatment-related.

CONCLUSIONS

- The pharmacokinetics of SKP-1041 were similar with day and night administration.
- Proof-of-concept for sleep maintenance was observed in the second noise period at zaleplon C_{max}.
- SKP-1041 was well-tolerated.

REFERENCES

1. 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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