

# PHARMACODYNAMIC PROFILE OF THREE NOVEL RELEASE FORMULATIONS OF ZALEPLON IN NORMAL VOLUNTEERS AS EVALUATED BY THE MULTIPLE SLEEP LATENCY TEST

James Walsh<sup>1</sup>, Corinne Staner<sup>2</sup>, Anne Tisserant<sup>2</sup>, Rémy Luthringer<sup>2</sup>, Luc Staner<sup>2</sup>

1. St Luke's Hospital, Chesterfield, MO, USA; 2. Forenap Pharma, Rouffach, France

## INTRODUCTION

The Multiple Sleep Latency Test (MSLT) is a well-validated, standardized measure of physiologic sleep tendency. The MSLT was used in this phase I study to evaluate the effects of daytime administration of three novel formulations of zaleplon on the sleep tendency of healthy normal volunteers.

## OBJECTIVE

To assess sleep tendency using the MSLT after daytime administration of three novel formulations of zaleplon 15 mg compared to placebo and the standard formulation of zaleplon.

## SUBJECTS

- Healthy volunteers meeting the following entry criteria were enrolled:
  - Inclusion criteria: 20 – 50 years of age; good general health; body mass index 18 – 30 kg/m<sup>2</sup>; females practicing effective birth control, surgically sterile, or ≥12 months postmenopausal.
  - Exclusion criteria: 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 xanthine-containing drinks >500 mg/day of caffeine. Patients were also excluded if mean MSLT at screening was <10 minutes with one sleep latency <8. The screening MSLT consisted of 5 nap opportunities of 20 minutes maximum, performed at 2-hour intervals.

## METHODS

- 5-arm crossover, single-dose comparison of zaleplon 15 mg in release formulations A, B, C (Table 1), placebo (matched to three formulations), and unblinded commercially available immediate-release zaleplon 10 mg (I-RZ).
- The Geoclock<sup>®</sup> (SkyePharma, London, UK) delivery system, a unique technology that allows delivery of a drug over a preset time period, was used to provide the three different zaleplon 15 mg release characteristics.
- Each treatment arm was separated by a 4-7 day washout period. During each treatment subjects had three assessments predose (-20, -12, -1 hours) and each hour for 12 assessments postdose; plasma drug concentrations were also measured at the postdose time points. Study drug was administered at 9:00 AM.

## STATISTICAL ANALYSIS

Postdose differences between each formulation and placebo or I-RZ were described with a mixed model on change from baseline. MSLT baseline was the mean of the three predose assessments at -20, -12, and -1 hours.

Table 1. Release characteristics of zaleplon 15 mg formulations A, B, and C.

Formulation	Delay from ingestion to active drug release	Characteristics of drug release
A	2 hours	Immediate release
B	2 hours	2-hour controlled release
C	1 hour	4-hour controlled release

## RESULTS

- Nineteen healthy volunteers (13 female, 6 male); ages 21-46.
- MSLT changes with placebo administration followed the known circadian time course: shortest MSLT 5 hours postdose, with increased MSLT thereafter, peaking 11 hours postdose. Significant treatment differences versus placebo ( $p \leq 0.05$ ) were noted for A (hours 2-4), B (hours 2-4), and C (hours 1-4) (Figure 1 and Table 2).
- As compared to I-RZ 10 mg, sleep latencies were significantly shorter for formulations A ( $p < 0.01$ ) and B ( $p < 0.05$ ) 4 hours postdose.
- Sleep latencies increased from 5-12 hours postdose and were comparable among all treatments. Changes in MSLT paralleled plasma drug concentrations (Figure 2).

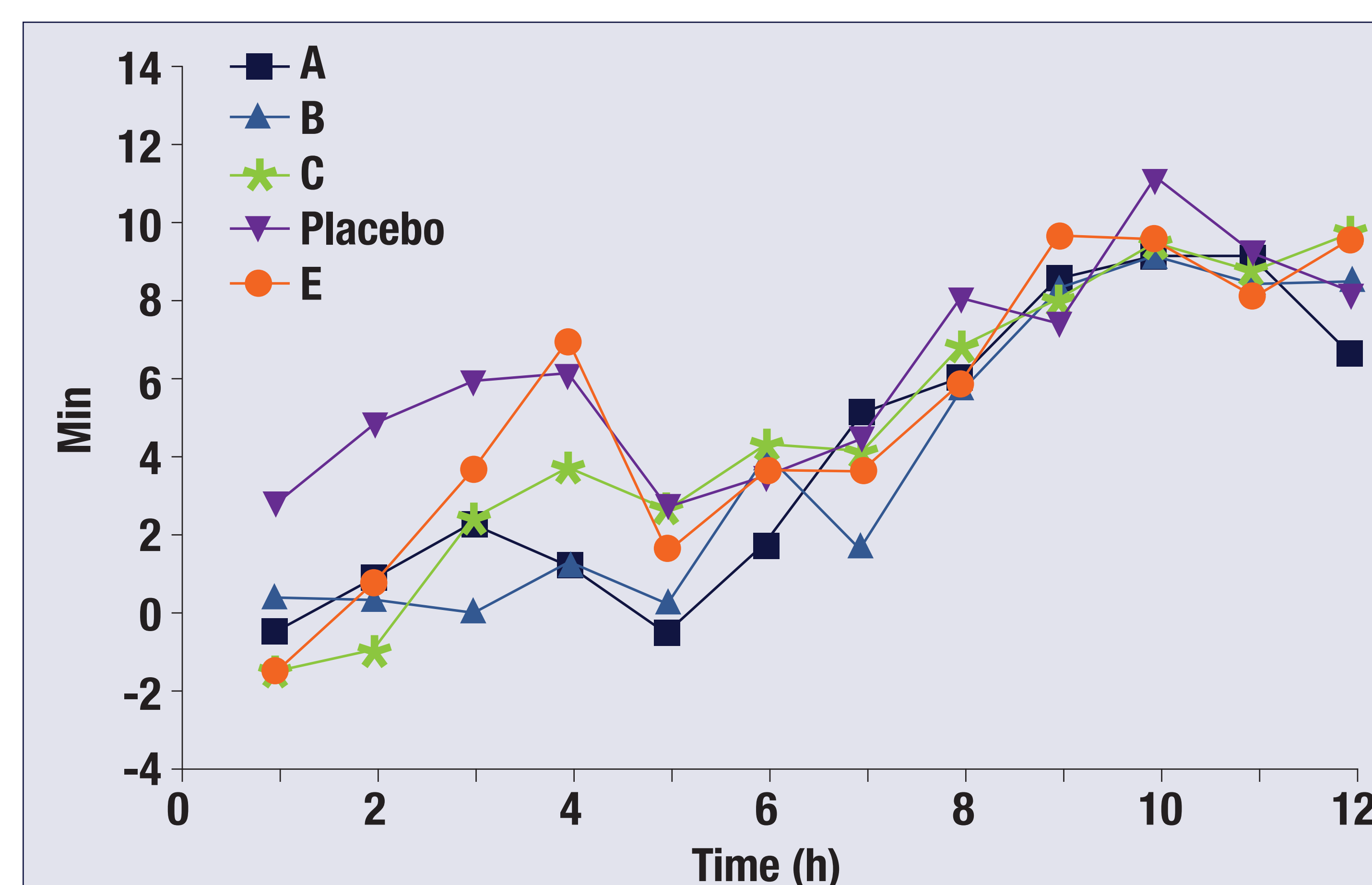


Figure 1. Plot over time of change from baseline values of sleep onset latencies at each time point during the five treatment conditions.

Table 2. Summary of placebo to drug differences for MSLT latencies during the first 4 time points postdose. Significant decreases of sleep onset latencies are indicated by ↓↓ if  $p < 0.01$  and ↓ if  $p < 0.05$ .

Treatment	Time Post-Dose			
	1 hour	2 hours	3 hours	4 hours
I-RZ	↓↓	↓	↔	↔
A	↔	↓	↓	↓↓
B	↔	↓	↓↓	↓
C	↓	↓↓	↓	↓

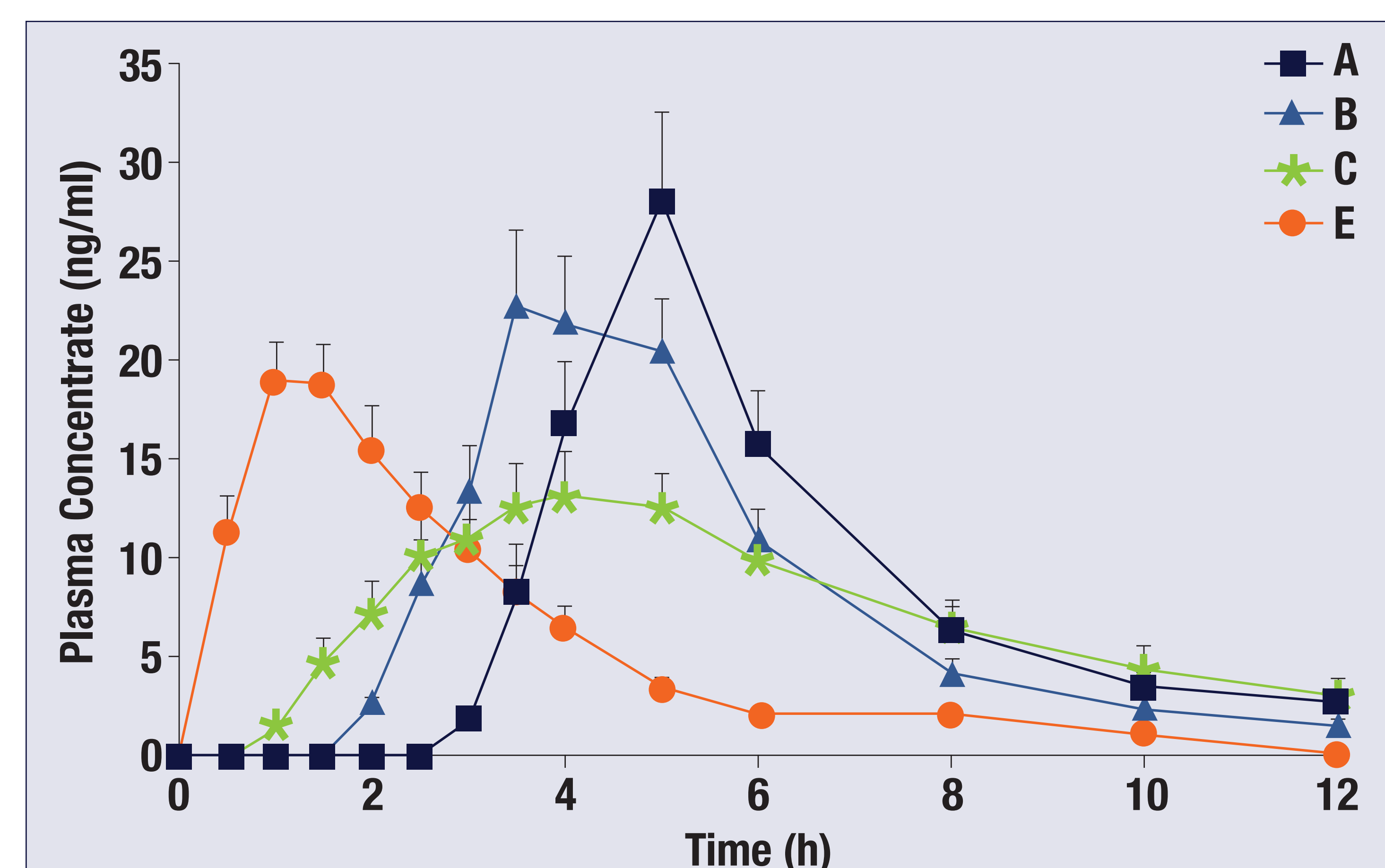


Figure 2. Mean plasma concentrations over time for zaleplon 15 mg formulations A, B, C, and I-RZ 10 mg (E). Figure includes standard error bars ( $\pm$ SE).

## CONCLUSIONS

- The three novel formulations of zaleplon 15 mg resulted in significantly increased sleep tendency versus placebo and I-RZ during the 1 to 4 hours postdose time period.
- The profiles indicated differing time courses of sleep-promoting activity which corresponded to plasma drug levels.

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