

# PHARMACOKINETIC PROFILE OF SINGLE ORAL DOSES OF ZALEPLON IN THREE NOVEL FORMULATIONS IN NORMAL VOLUNTEERS

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## INTRODUCTION

Zaleplon is a nonbenzodiazepine hypnotic currently available as a 10 mg immediate-release capsule for the treatment of insomnia. Zaleplon is effective for sleep-induction without unwanted residual effects, the result of a pharmacokinetic profile characterized by rapid absorption and rapid elimination.<sup>1-3</sup>

The pharmacokinetics of zaleplon were evaluated when administered by a new controlled-release oral drug delivery system. The Geoclock® (SkyePharma, London, UK) delivery system is a chronotherapy-focused press coated tablet with active drug loaded inside an outer tablet layer formulated to obtain a pH-independent lag time prior to core drug delivery.

## OBJECTIVE

To investigate the pharmacokinetic profile of zaleplon when administered by the Geoclock drug delivery system.

## METHODS

- Phase I, double-blind, randomized, placebo-controlled, crossover study in healthy volunteers.
- Inclusions: 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.
- 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 xanthine-containing drinks >500 mg/day of caffeine.
- Study drug: Single oral doses of zaleplon 15 mg in three formulations (A, B, C) with different release characteristics (Table 1); placebo tablets looked identical to study drug; immediate-release marketed zaleplon (10 mg; I-RZ) was included as an open comparator arm.

**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

- Study drugs administered at approximately 9:00 AM; subjects remained in bed.
- Blood samples were drawn predose and at 13 time points up to 12 hours postdose.

- Crossover administrations were separated by a 4- to 7-day washout period.
- Pharmacokinetic parameters: lag time ( $T_{lag}$ , time from administration to first quantifiable concentration), peak plasma concentration ( $C_{p1_{max}}$ ), time from administration to  $C_{max}$  ( $T_{max}$ ), elimination half-life ( $T_{1/2}$ ), and area under the plasma concentration-time curve (AUC) to the time of last quantifiable concentration ( $AUC_{0-t}$ ) and AUC from time zero to infinity ( $AUC_{0-inf}$ ).

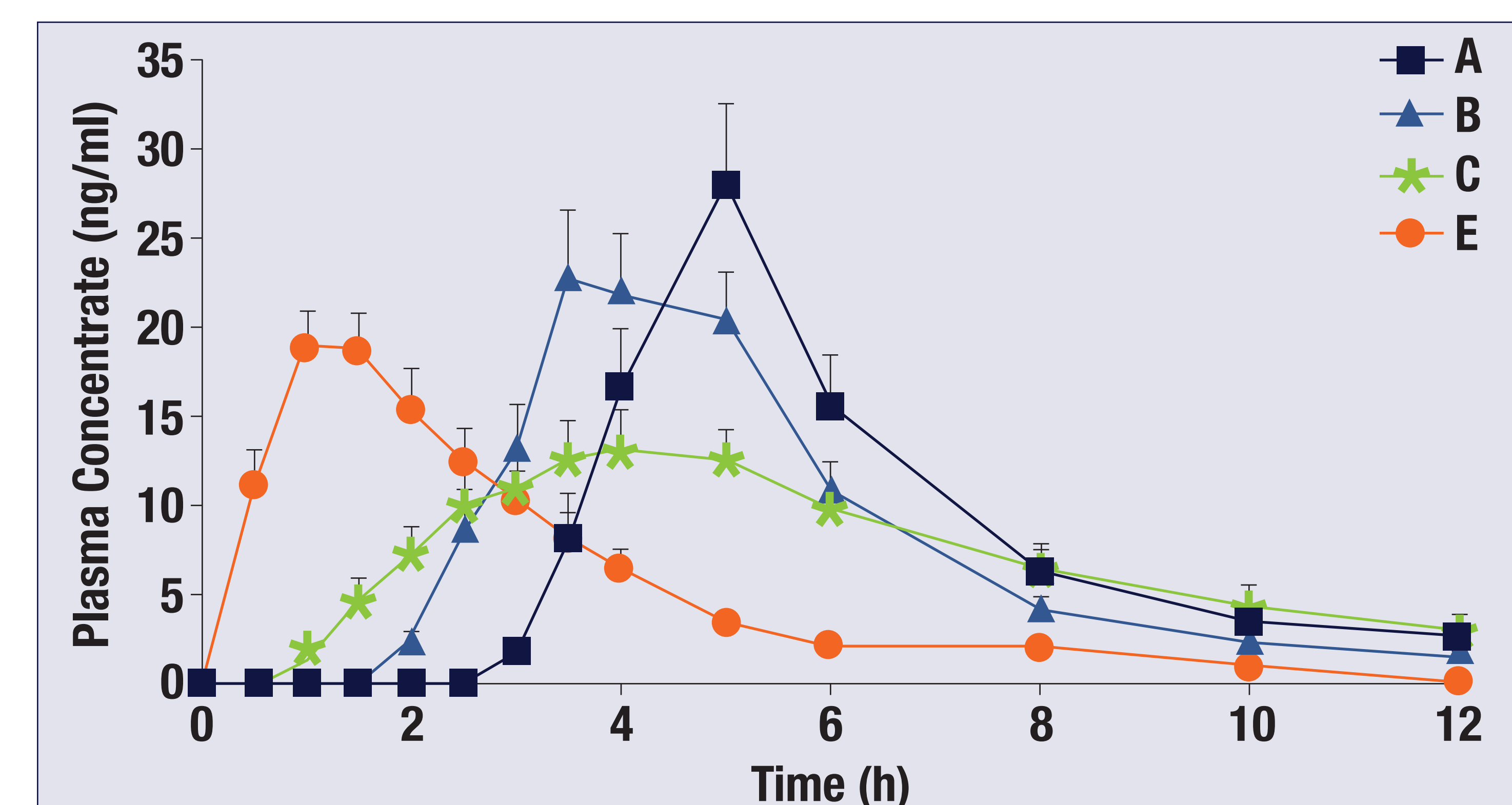
## RESULTS

- 19 healthy volunteers (13 female, 6 male; ages 21-46) completed the study in compliance with protocol. One subject discontinued the study.
- Relative bioavailabilities for A, B, and C vs I-RZ were 98%, 97%, and 93%, respectively, for  $AUC_{0-t}$ , and 99%, 97%, and 83%, respectively, for  $AUC_{0-inf}$ .
- Table 2 summarizes pharmacokinetic profiles of study formulations and I-RZ.

**Table 2. Summary of pharmacokinetic variables after administration of zaleplon 15 mg formulations A, B, C, and I-RZ 10 mg.**

Median	A	B	C	I-RZ 10 mg
$t_{lag}$ (hr)	3.0 n = 19	2.0 n = 19	1.0 n = 20	0.0 n = 19
$t_{max}$ (hr)	5.0 n = 19	3.9 n = 19	3.9 n = 20	1.5 n = 19
Arithmetic Mean [±SD]	A	B	C	I-RZ 10 mg
$t_{lag}$ (hr)	3.1 [±0.3] n = 19	1.9 [±0.3] n = 19	1.2 [±0.5] n = 20	0.0 n = 19
$C_{p1_{max}}$ (ng/mL)	32.4 [±18.8] n = 19	27.0 [±15.1] n = 19	16.6 [±9.1] n = 20	25.0 [±11.9] n = 19
$t_{max}$ (hr)	4.9 [±1.0] n = 19	4.1 [±0.7] n = 19	3.9 [±0.9] n = 20	1.5 [±0.8] n = 19
$t_{1/2}$ (hr)	1.5 [±0.3] n = 17	1.4 [±0.4] n = 18	1.8 [±0.4] n = 11	1.2 [±0.2] n = 14
$AUC_{0-t}$ (ng•h/mL)	83.2 [±53.0] n = 19	83.1 [±45.7] n = 19	79.5 [±57.0] n = 20	59.8 [±26.0] n = 19
$AUC_{0-inf}$ (ng•h/mL)	90.2 [±57.0] n = 17	87.7 [±46.9] n = 18	75.4 [±27.1] n = 11	60.5 [±30.0] n = 14

- Plasma concentrations of zaleplon were quantifiable for 10-12 hours after administration with formulations A, B, and C. (Figure 1)



**Figure 1. Mean plasma concentrations over time for zaleplon 15 mg formulations A, B, C, and I-RZ 10 mg (E). Figure includes standard error bars (±SE).**

- No differences were noted between males and females.

## SAFETY

- All formulations were well-tolerated; no clinically relevant changes in vital signs, laboratory parameters, or physical examination were noted.
- 13 adverse events (including 2 with placebo) were considered related to study drug administration; the majority were mild/moderate and self-limiting.
- One subject reported moderate/severe anxiety and a moderate increase in blood pressure after receiving formulation C in the first study period and was discontinued from the study.
- Most related adverse events were reported when subjects received I-RZ.

## CONCLUSIONS

- Three novel formulations of zaleplon provided consistent active drug concentrations at different time points after administration with rapid decline after  $T_{max}$ .
- The three novel formulations of zaleplon allowed more prolonged exposure to active drug than I-RZ.
- Pharmacokinetic profiles differed between formulations and the active comparator, but were similar within study-drug arms.
- Further study of the clinical implications for zaleplon 15 mg in a novel release formulation is warranted.

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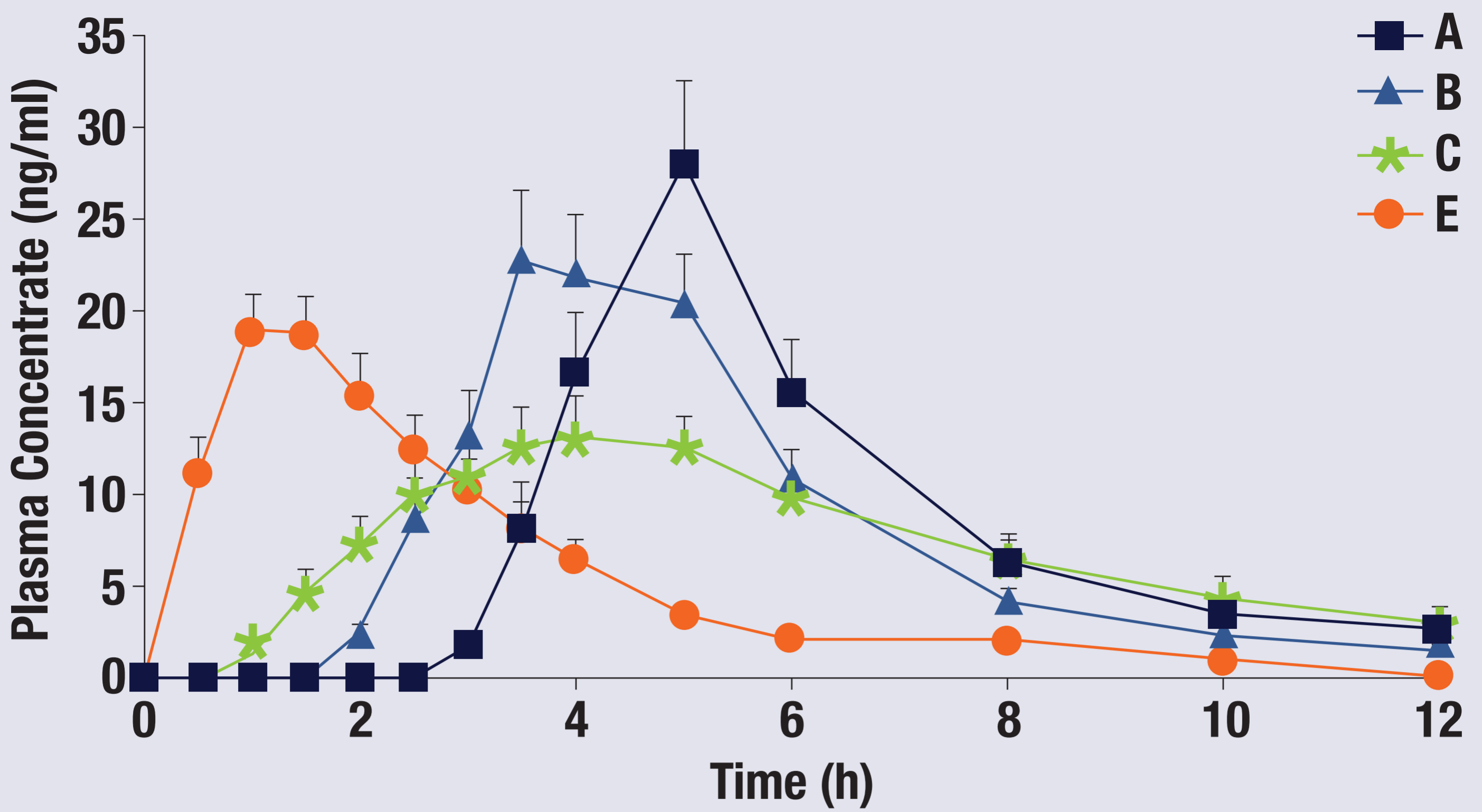
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<b>Arithmetic Mean [<math>\pm</math>SD]</b>	<b>A</b>	<b>B</b>	<b>C</b>	<b>I-RZ 10 mg</b>
$t_{lag}$ (hr)	3.1 [ $\pm$ 0.3] n = 19	1.9 [ $\pm$ 0.3] n = 19	1.2 [ $\pm$ 0.5] n = 20	0.0 n = 19
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$t_{1/2}$ (hr)	1.5 [ $\pm$ 0.3] n = 17	1.4 [ $\pm$ 0.4] n = 18	1.8 [ $\pm$ 0.4] n = 11	1.2 [ $\pm$ 0.2] n = 14
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