

PHARMACODYNAMIC PROFILE OF THREE NOVEL RELEASE FORMULATIONS OF ZALEPLON VERSUS PLACEBO AND MARKETED ZALEPLON MEASURED BY ELECTROENCEPHALOGRAPHY AND THE KAROLINSKA DROWSINESS TEST IN HEALTHY VOLUNTEERS

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INTRODUCTION

Zaleplon is a commercially available non-benzodiazepine agent with a very short half-life (1 hour), very little addiction potential, and little or no residual hypnotic effect upon waking.¹⁻⁴ It is currently being used (since 2000) for sleep induction, but because of its short half-life, it is not routinely used for sleep maintenance.

The pharmacodynamic profile of zaleplon when administered over different time periods was evaluated in a phase I study in healthy volunteers. To provide the differences in administration, the study utilized the Geoclock® (SkyePharma, London, UK) delivery system, a unique technology that allows delivery of a drug over a preset time period.

OBJECTIVE

The aim of this study was to assess the pharmacodynamic profile of three formulations of zaleplon on the central nervous system of healthy volunteers over a 12-hour period using 4-lead electroencephalography (EEG) and the Karolinska Drowsiness Test (KDT), compared to marketed zaleplon and placebo.

METHODS

- Twenty healthy subjects between 20 and 50 years old were enrolled in this double-blind, placebo-controlled, 5-way cross-over study, including an open label positive control arm.
- On Day 1 of the first treatment period, subjects were randomised to receive 15 mg of zaleplon tablet formulations A, B, or C (Table 1), 10 mg of immediate-release marketed zaleplon capsule (IR-Z) or placebo tablet. Study drugs were administered at approximately 9:00 AM after which subjects remained in bed.
- A washout period of at least 4 days was included between consecutive periods.
- EEG and KDT were obtained predose and for 12 hours postdose (Table 2). Drug plasma levels were obtained at the same times.
 - EEG parameters were calculated on the median of the 4 lead couples (F4-T4, F3-T3, T4-O2, T3-O1). Spectral analyses were done to obtain absolute powers of beta, alpha, theta, delta and a sensitive measure for arousal: the alpha-slow-wave index (ASI), defined as [alpha power / (delta + theta powers)].
 - For the KDT, delta, theta, alpha and beta powers were calculated from 3 lead pairs (Fz-Cz, Cz-Pz, Pz-Oz) during 2 conditions (eyes open and eyes closed) and an alpha attenuation coefficient (eyes-closed alpha power / eyes-open alpha power) was determined.
- Differences between each formulation and placebo or IR-Z were studied with a mixed model on change from baseline values to determine whether the treatment affects the pharmacodynamic assessments and whether there is an interaction between treatment effect and time effect.

Table 1. Release characteristics of zaleplon 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

Table 2. Investigational schedule per period for EEG and KDT

Time pre- or postdose (hr)	Day -1		Day 1													
	-20	-12	-1	0	1	2	3	4	5	6	7	8	9	10	11	12
Time			8 AM	9 AM	10 AM	11 AM	12 PM	1 PM	2 PM	3 PM	4 PM	5 PM	6 PM	7 PM	8 PM	9 PM
Drug administration				X												
4-lead EEG	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
KDT	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Drug plasma levels*			X		X	X	X	X	X	X	X	X	X	X	X	X

*Drug plasma levels also measured 0.5, 1.5, 2.5, and 3.5 hours post-dose.

RESULTS

- EEG and KDT results for 18 subjects (12 females, 6 males; 21-46 years) are reported.
- No significant treatment effect or significant treatment x time interaction were observed for EEG delta or theta absolute powers.
- Significant treatment effects were noticed for ASI ($p < 0.001$), absolute power in the alpha band ($p < 0.001$), and total absolute power ($p = 0.008$). Treatment x time interaction was also significant for all formulations for these parameters ($p < 0.001$, $p < 0.001$, $p = 0.004$, respectively). Formulations A, B, and C globally decreased these EEG parameters 3, 4, and 5 hours after administration compared to placebo and IR-Z (Figures 1, 2, 3). As expected, the action of IR-Z was quickly visible after administration.

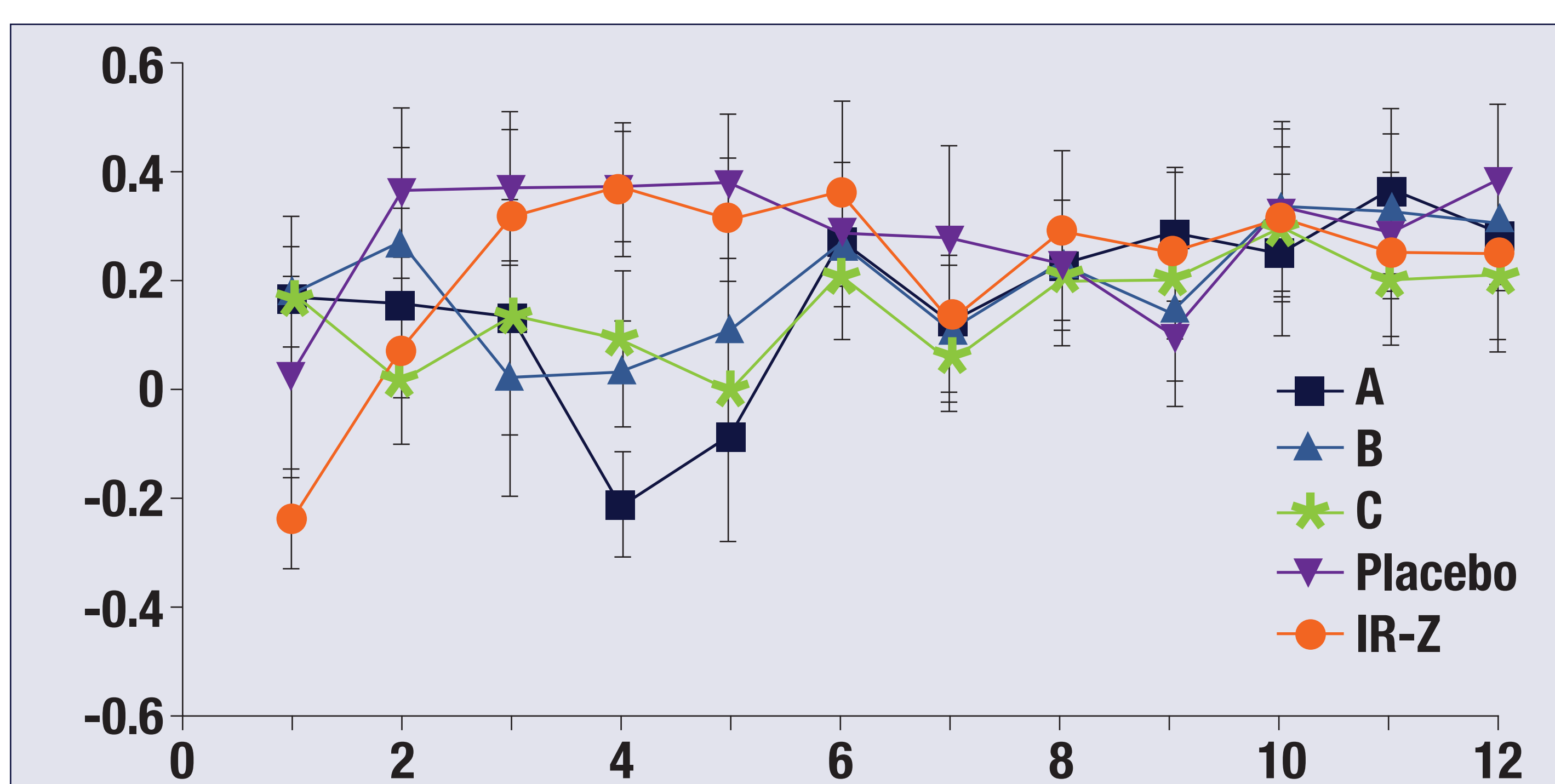


Figure 1. Mean (\pm SE) change from baseline over time for ASI (μV^2).

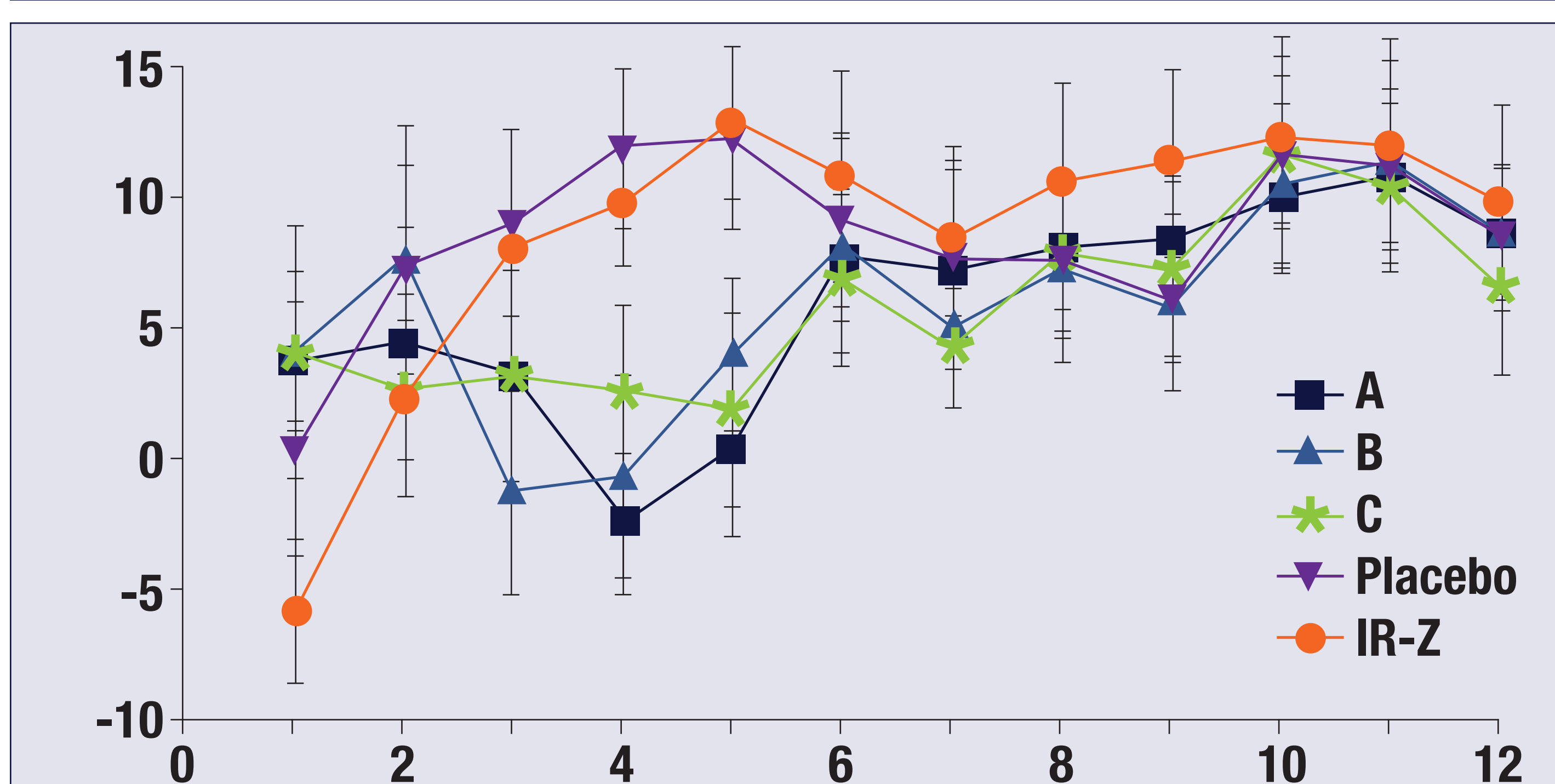


Figure 2. Mean (\pm SE) change from baseline over time for absolute power in the alpha band (μV^2).

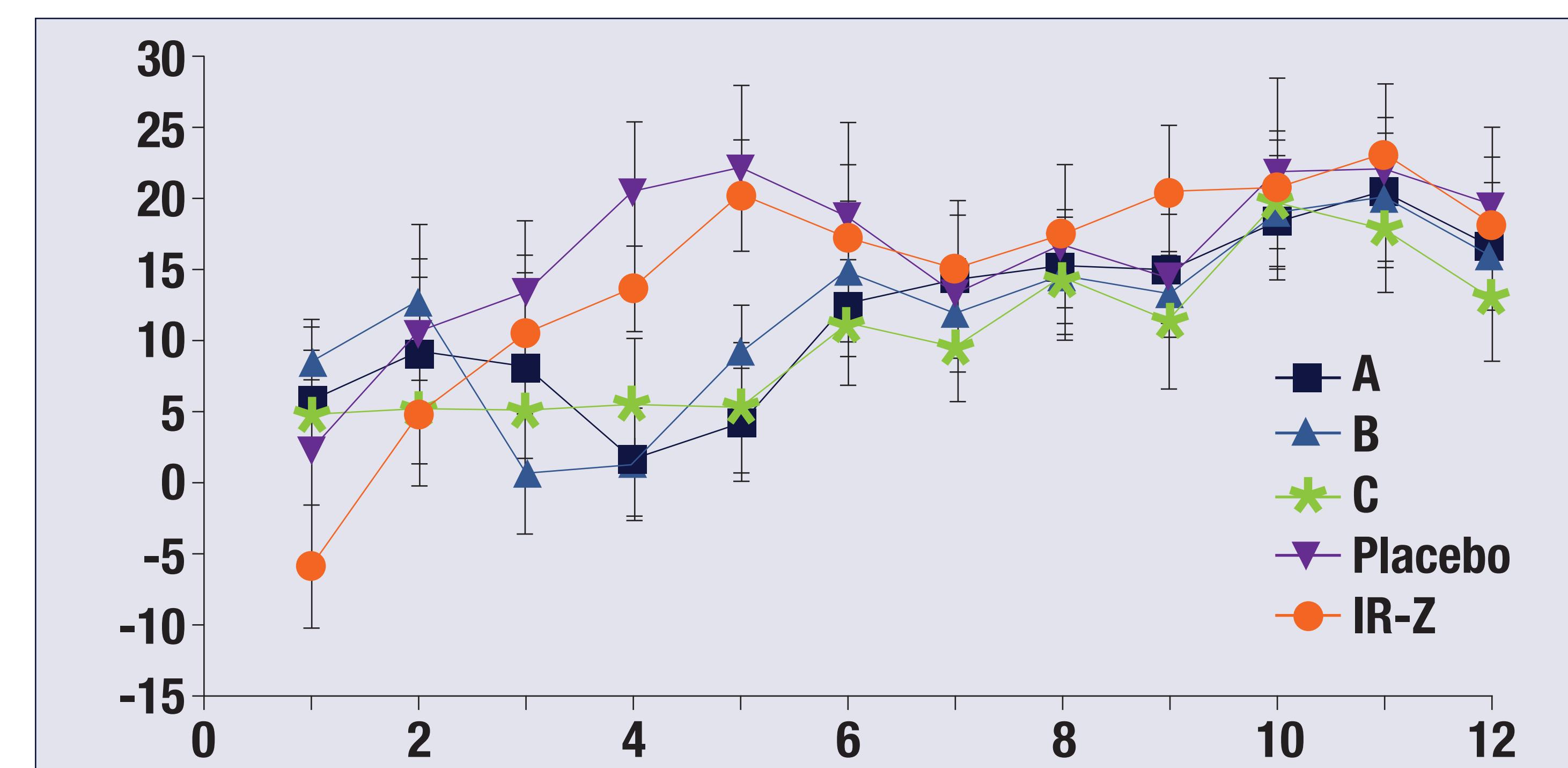


Figure 3. Mean (\pm SE) change from baseline over time for total absolute power (μV^2).

- KDT parameters correlated with EEG with the greatest sleepiness generally noted at the same periods of time.
- Results for EEG and KDT corresponded to drug plasma levels, which peaked between 3.9 and 4.9 hours postdose for the three formulations and 1.5 hours for IR-Z. EEG and KDT parameters were comparable to placebo 8 hours postdosing.

CONCLUSION

The three formulations showed maximum sedation 3 to 5 hours post-administration as demonstrated by mean changes in EEG and KDT. No residual effects were observed for these formulations after 8 hours post-administration.

REFERENCES

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KDT	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X
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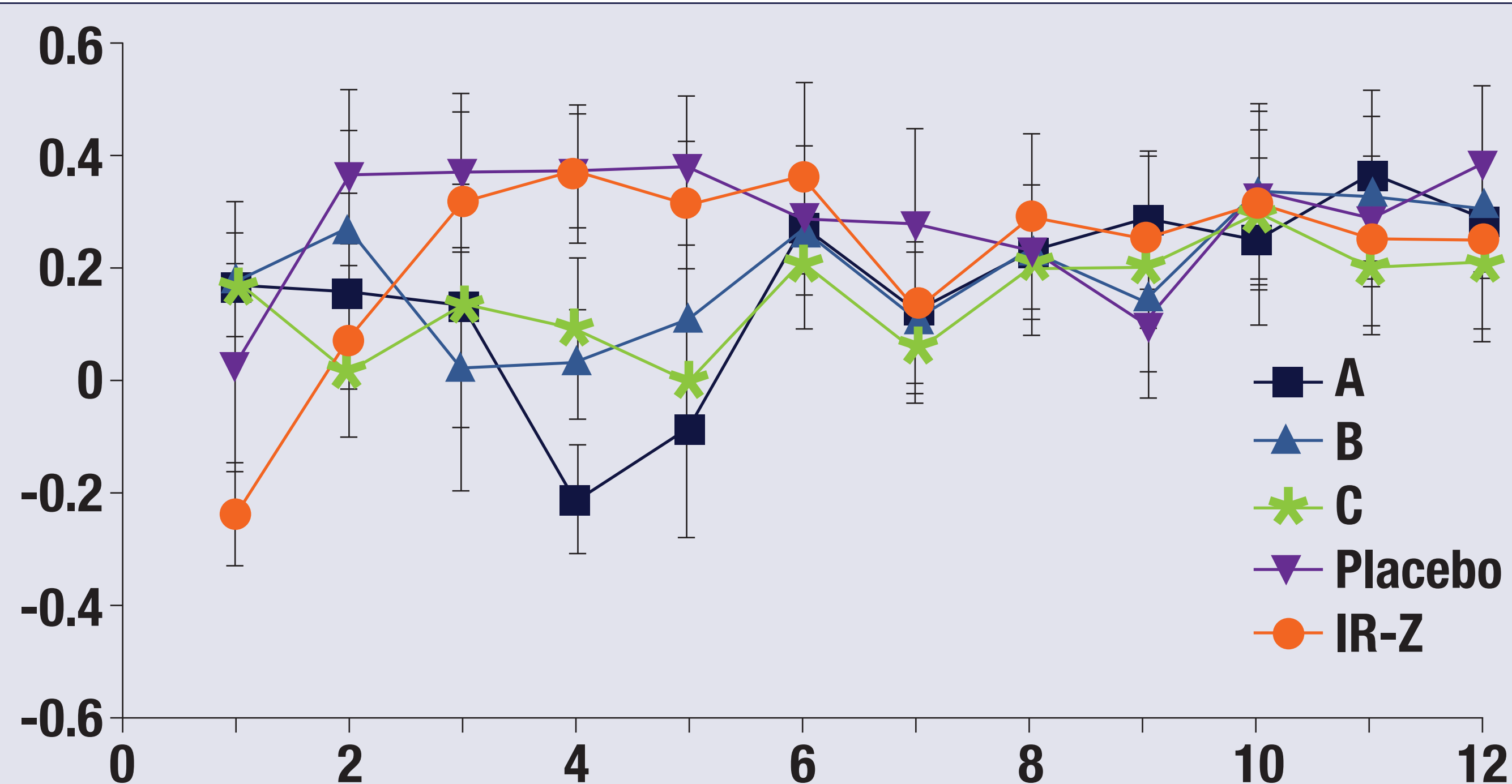


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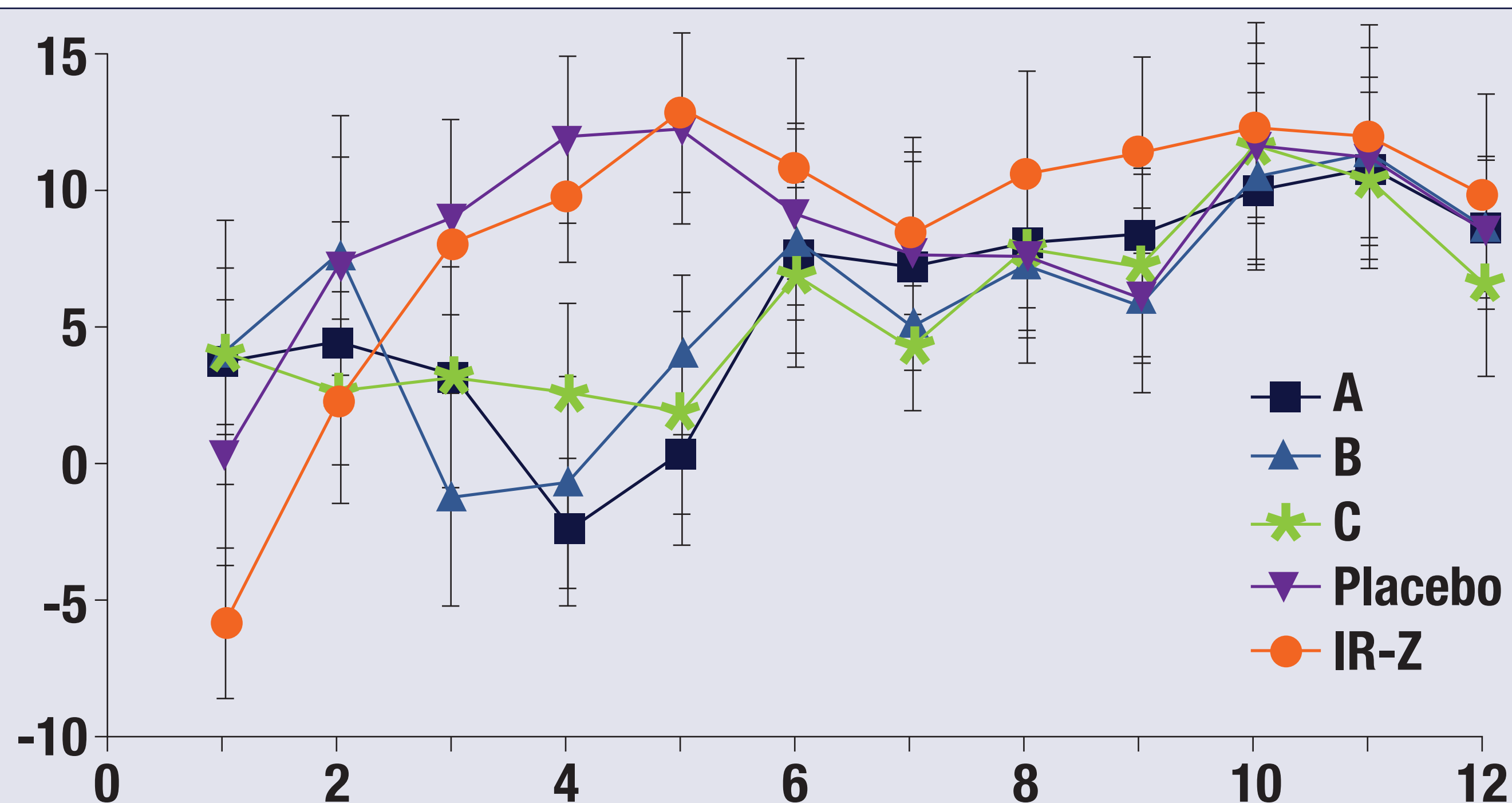


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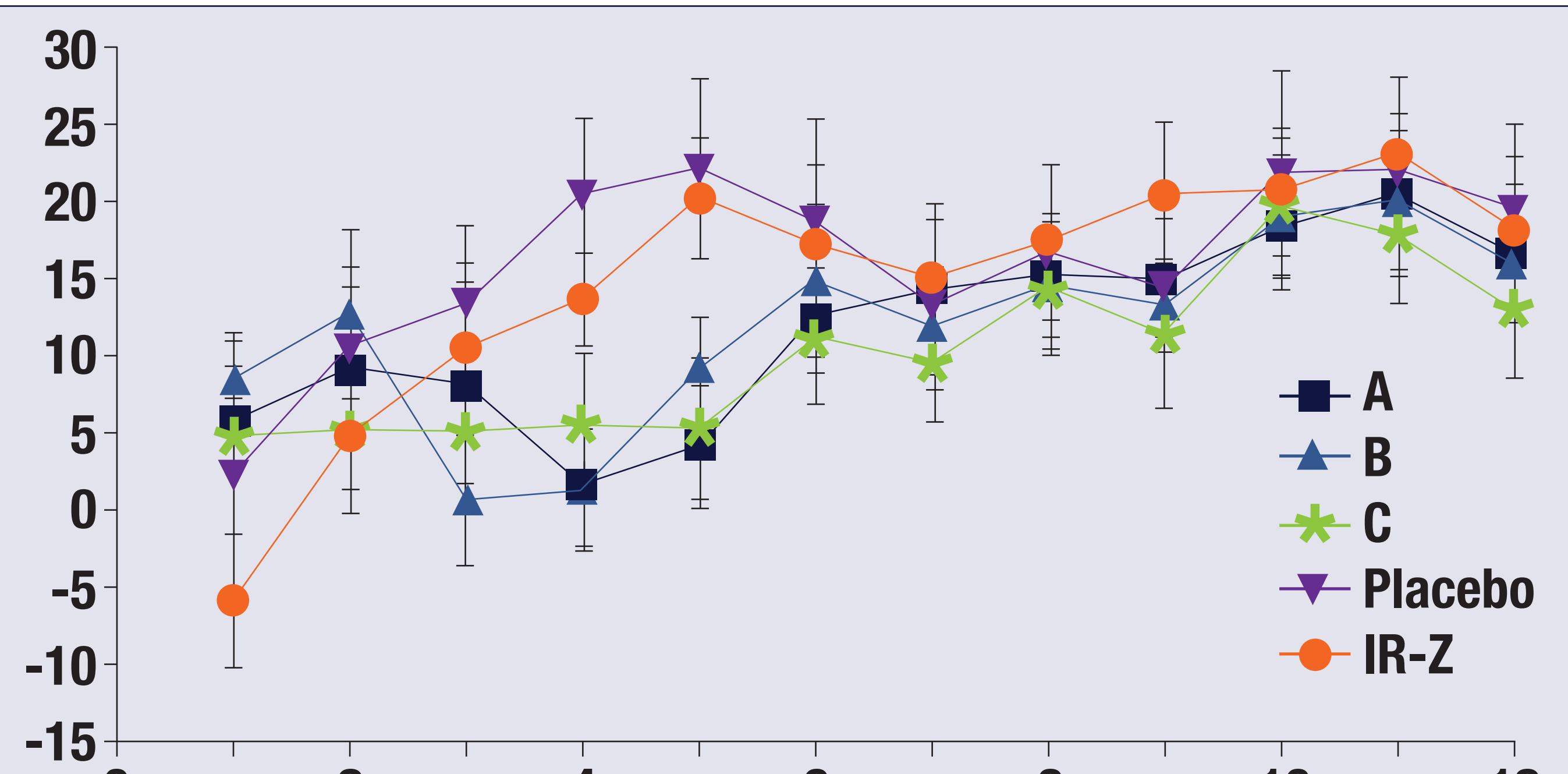


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