

USE OF THE ADDICTION RESEARCH CENTER INVENTORY (SEDATION SUBSCALE) AND THE KAROLINSKA SLEEPINESS SCALE TO EVALUATE SUBJECTIVE ALERTNESS AFTER SINGLE ORAL DOSES OF ZALEPLON IN THREE NOVEL RELEASE FORMULATIONS

Nathalie Pross, Luc Staner, Rémy Luthringer, Corinne Staner
Forenap Pharma, Rouffach, France

INTRODUCTION

Zaleplon is a non-benzodiazepine agent with very little addiction potential and little or no residual hypnotic effect upon waking. It is currently being used for sleep induction, but due to its very short half-life (1 hour), it is not routinely used for sleep maintenance. The aim of this presentation is to examine the changes in subject-perceived alertness after morning administrations of placebo, marketed zaleplon and three novel delayed and controlled-release formulations of zaleplon.

Different assessment methods are used in clinical trials to evaluate subjective effects of drugs; the Addiction Research Center Inventory (ARCI-49) and the Karolinska Sleepiness Scale (KSS) were used here. The main objectives of these assessments were i.) to determine if differences in subjective feeling of alertness could be evidenced between the three novel formulations of zaleplon and marketed zaleplon or placebo, and ii.) to show if differences in the time course of subjective alertness could be observed among these three novel treatments.

OBJECTIVE

To assess sleepiness using the ARCI-49 and KSS after administration of three novel formulations of zaleplon 15 mg.

SUBJECTS AND METHODS

- Study design: phase I, double-blind, crossover, placebo and open-labeled marketed immediate-release zaleplon (10 mg) controlled, single-center study. The administration of each study drug was separated by a 4- to 7-day washout period.
- Participants: 19 healthy volunteers (13 woman, 6 men; ages 21-46 years) were enrolled. None of them presented a sleep disorder or disturbed sleep/wake patterns. Concomitant treatment was not allowed during the study and subjects had to be withdrawn for any medication within 14 days prior to admission (except paracetamol up to 3 g/day). The consumption of alcohol, tobacco, xanthine-containing drinks or caffeine was prohibited during the study.
- Treatments: single oral doses of zaleplon 15 mg in formulations A, B, and C with different release characteristics (Table 1), commercially-available 10 mg immediate-release zaleplon (I-RZ) and placebo were administered according to a randomized 5-way crossover design. Study medication was administered at 9:00 AM (± 15 min) after which subjects remained in bed for 12 hours under the supervision of the clinical staff.
- To provide differences in release characteristics, the study utilized the Geoclock[®] (SkyePharma, London, UK) delivery system, a unique technology that allows delivery of a drug over a preset time period.

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

- Subjective sleepiness evaluations:
 - The ARCI-49 is a 49-item “true-false” questionnaire developed specifically to measure subjective effects of drugs which have diverse pharmacological actions. The 49 items are divided into five empirically-derived subscales sensitive to specific pharmacological effects. Here the data concerning the PCAG (Pentobarbital Chlorpromazine Alcohol Group) subscale measuring sedation will be presented. The ARCI-49 was completed at T₀-1h (baseline), and at T₀+1h, T₀+3h, T₀+5h and T₀+8h after study drug administration.
 - The KSS is a self-rating scale assessing subjective sleepiness. The volunteer is asked to choose between nine different descriptions (1= very alert to 9 = very sleepy, great effort to keep awake, fighting sleep) to indicate sleepiness. The KSS was done at T₀-20h, T₀-12h and T₀-1h predose (mean = baseline), and every hour from T₀+1h to T₀+12h postdose.

RESULTS

ARCI-49 Sedation Subscale (PCAG)

- A significant ($p < 0.01$) treatment effect was observed for the PCAG subscale; when all time points were considered together, I-RZ led to the most sedated feeling while placebo led to the least. The comparisons between treatments indicated that some differences between formulations A, B, and C, and placebo or I-RZ appeared to be significant (Figure 1).

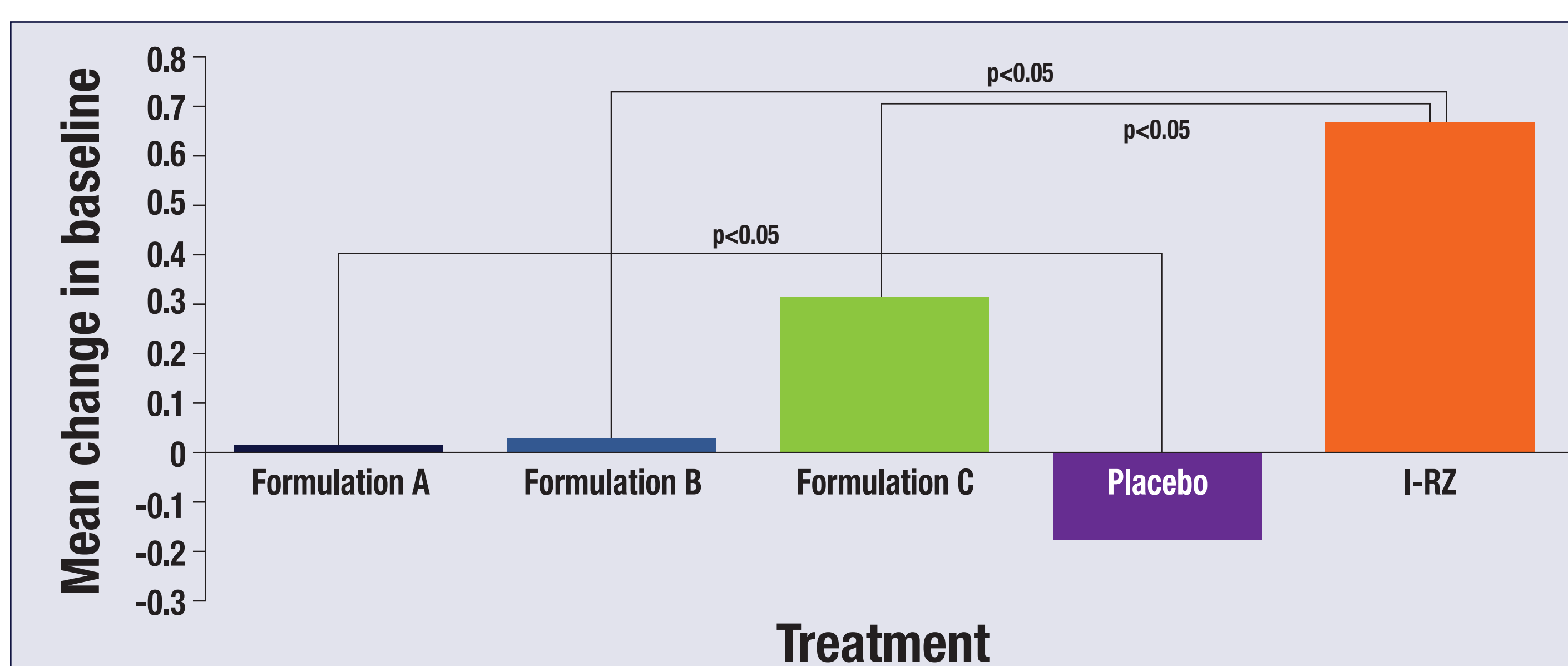


Figure 1. Mean changes from baseline between treatments for the sedation (PCAG) subscale of the ARCI-49.

- The treatment x time effect was not significant; during the day no difference in sedation among the treatments was noted.

Karolinska Sleepiness Scale

- A significant ($p < 0.001$) treatment effect was observed for the KSS; when all time points were considered together, sleepiness was greatest with I-RZ and least with placebo. The comparisons between treatments indicated that several differences between formulations A, B, and C, and placebo or I-RZ appeared to be significant (Figure 2).

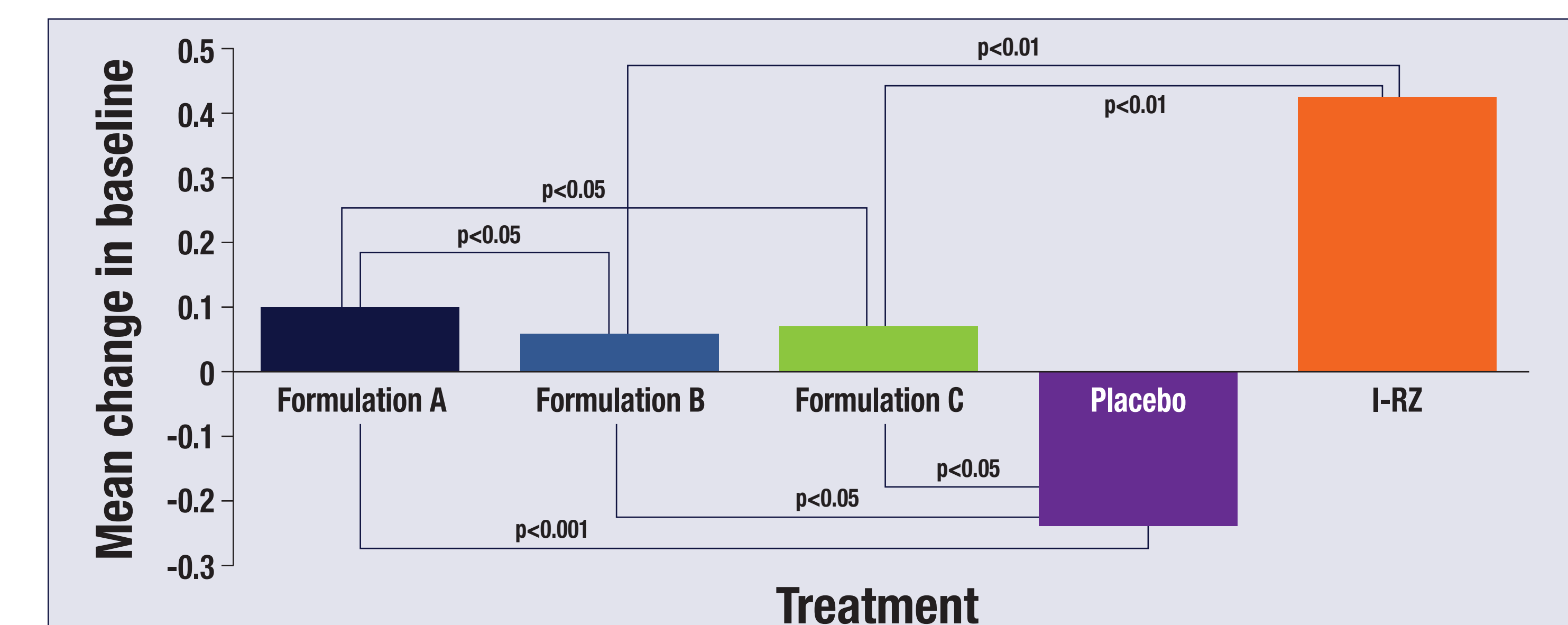


Figure 2. Mean changes from baseline between treatments in the KSS.

- A significant ($p < 0.001$) treatment x time effect was observed; subjective feelings of sleepiness varied significantly during the day and according to treatment. The comparisons between treatments at each time point indicated that the three formulations presented relatively different time-related profiles (Figure 3), nevertheless none of these novel treatments induced sleepiness after T₀+8h.

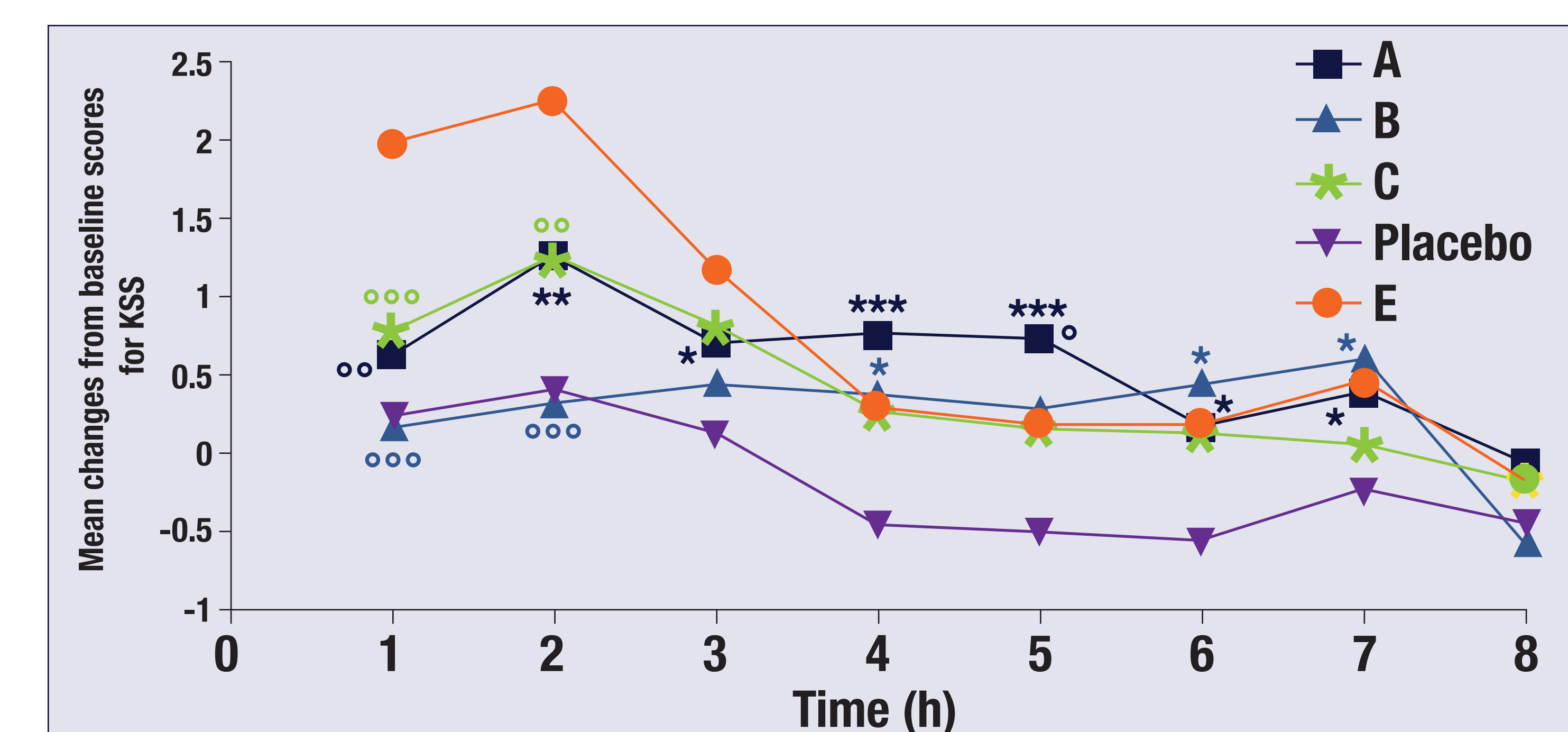


Figure 3. KSS: Comparisons between formulation A, formulation B, formulation C, placebo and I-RZ as a function of time. Significance between formulations and placebo: * $p < 0.05$; ** $p < 0.01$; * $p < 0.001$. Significance between formulations and I-RZ: o $p < 0.05$; oo $p < 0.01$; ooo $p < 0.001$.**

CONCLUSION

- Both subjective scales showed significant increases in subjective sedation and feeling of sleepiness with all novel formulations; all increases occurred at a later time postdose than with immediate-release zaleplon.

This study was supported by Somnus Therapeutics, Inc., Bedminster, NJ, USA.

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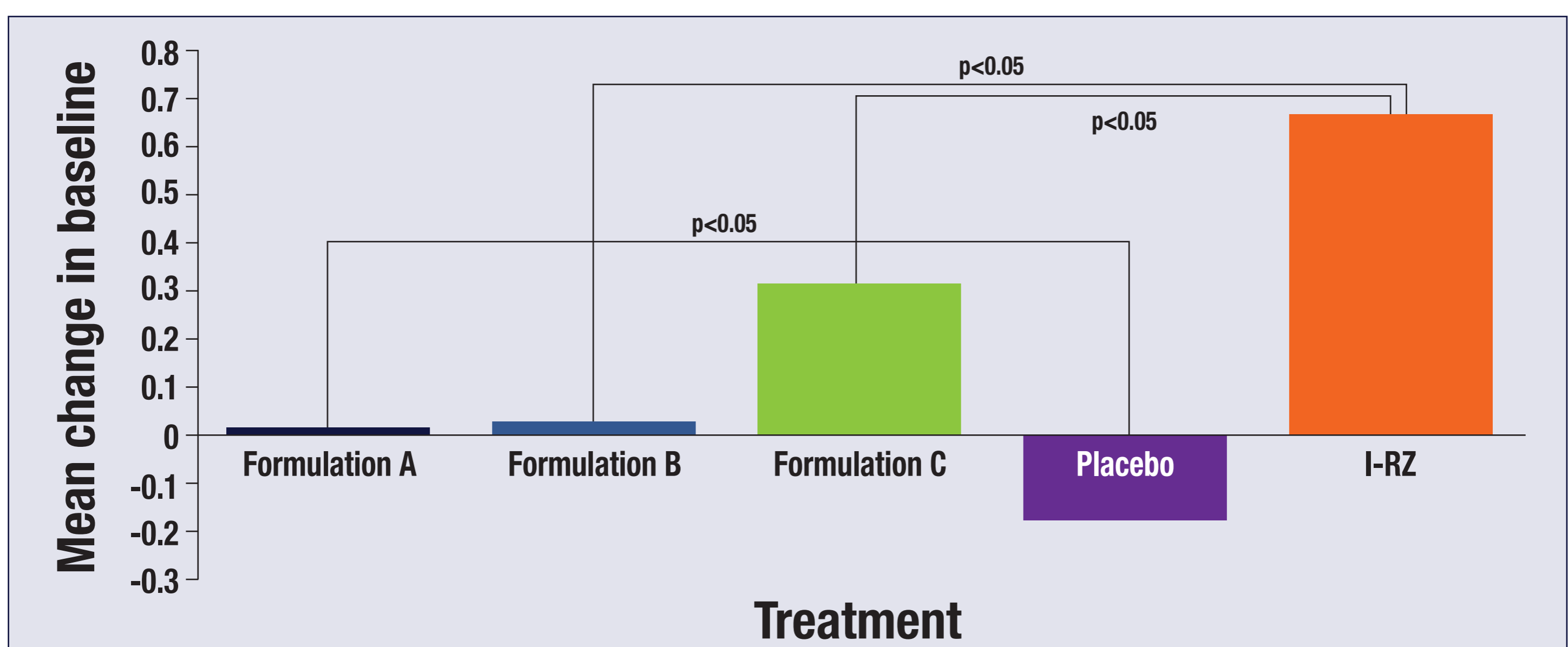


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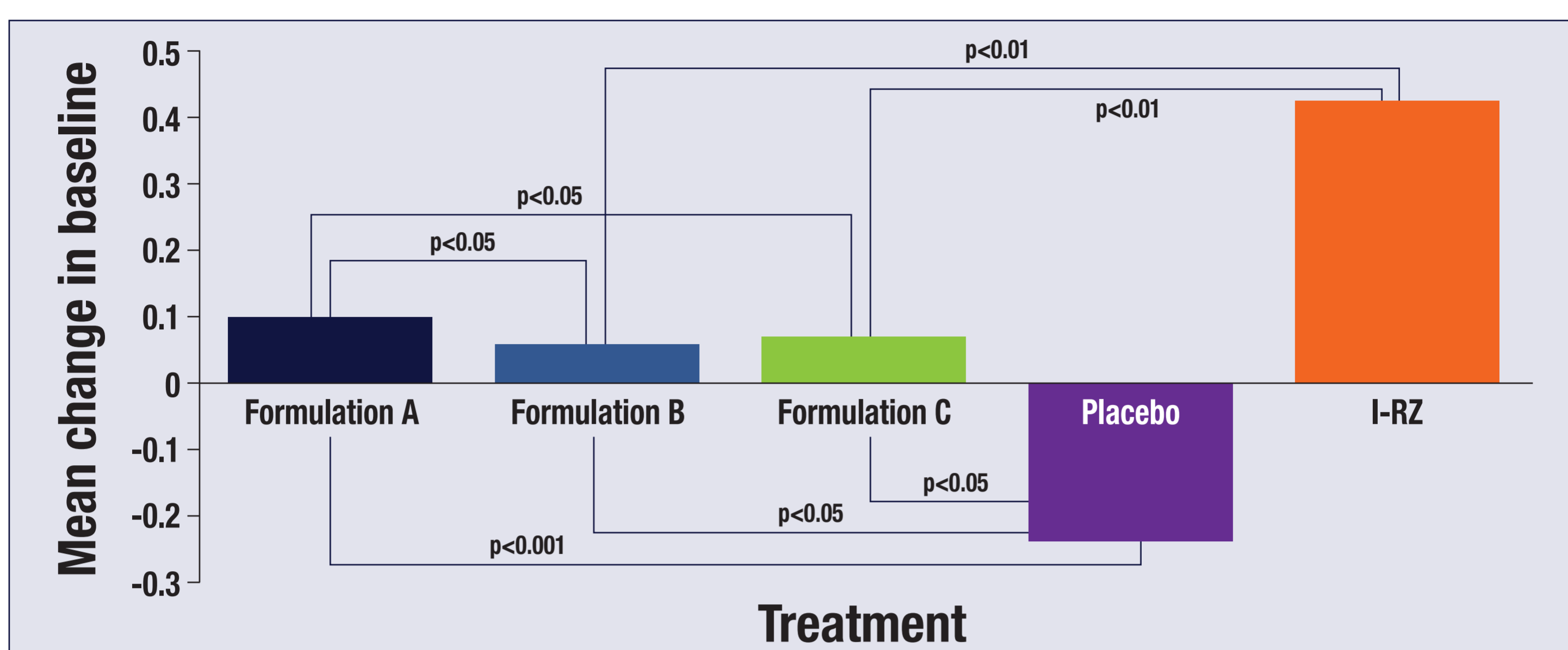


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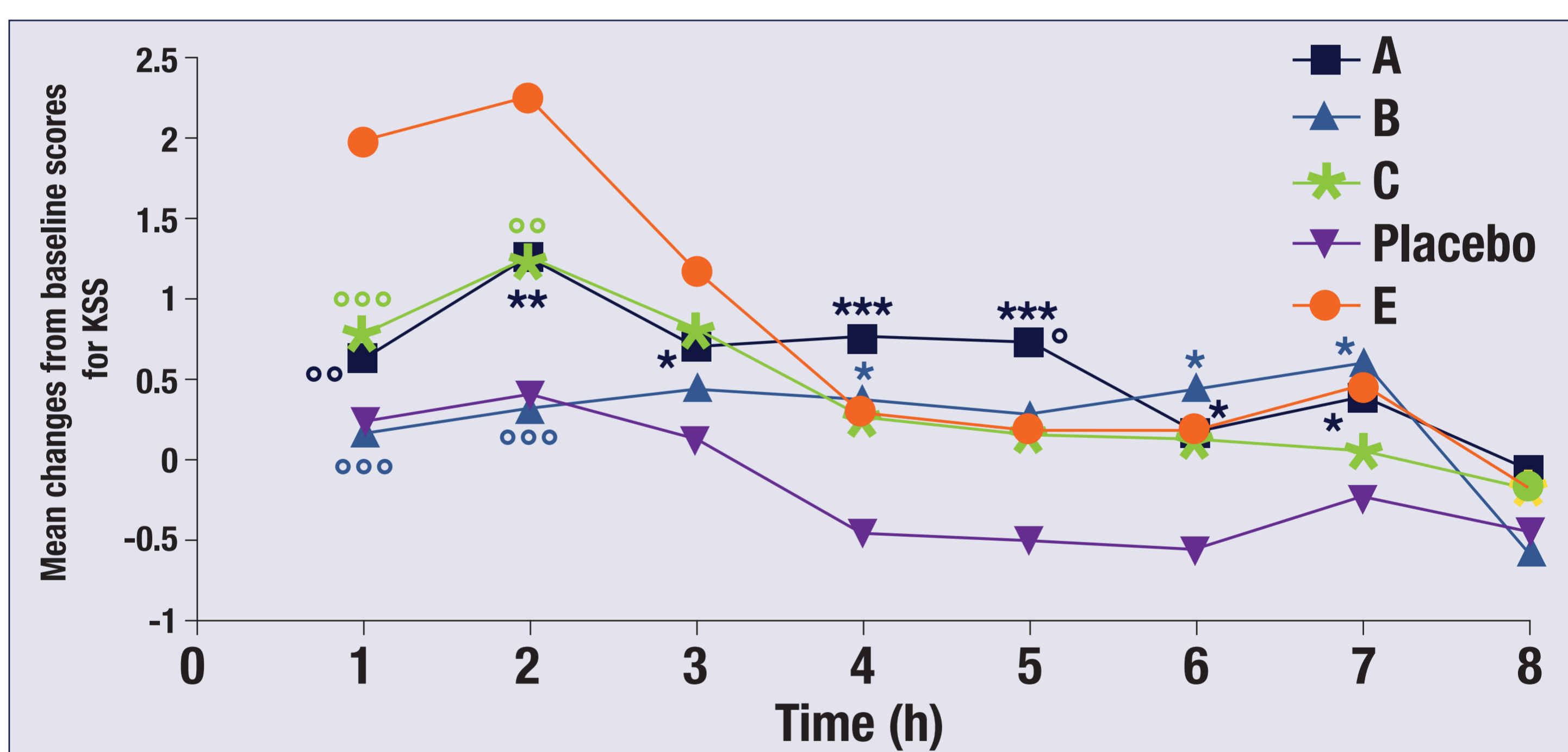


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