Comparative, Crossover PD Study of different formulations of extended release MPH

Thomas Spencer, MD, Principal Investigator
Joseph Biederman, MD, Co-Investigator
Massachusetts General Hospital

Ann Childress, MD, Co-Principal Investigator
Center for Psychiatry and Behavioral Medicine, Inc. Las Vegas, NV

Andrew Babiskin, PhD, Project Officer
& Lucy Fang, PhD
Division of Quantitative Methods and Modeling
Office of Research and Standards
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration

SV Faraone, SUNY Upstate Medical University, Syracuse, NY

Roberto Gomeni, Pharmacometrica, France.

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Dr. Spencer receives support from Royalties and Licensing fees on copyrighted ADHD scales through MGH Corporate Sponsored Research and Licensing.

Dr. Spencer has a US Patent (#14/027,676) for a non-stimulant treatment for ADHD and a US Patent Application pending (Provisional Number 61/233. 686), on a method to prevent stimulant abuse. Both through MGH corporate licensing

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The main aim of this randomized, placebo controlled, cross-over, analogue classroom study was to address the evaluation of bioequivalence in PD effects between extended release formulations of MPH with a similar PK profile (ascending curve) and intended duration of effect (12 hrs,) (e.g., OROS MPH profile; Concerta, Mallinckrodt generic).

For comparison purposes, we selected a compound with a different PK profile (more rapid early release) but similar intended duration of effect (12 hrs) (Quillivant XR).

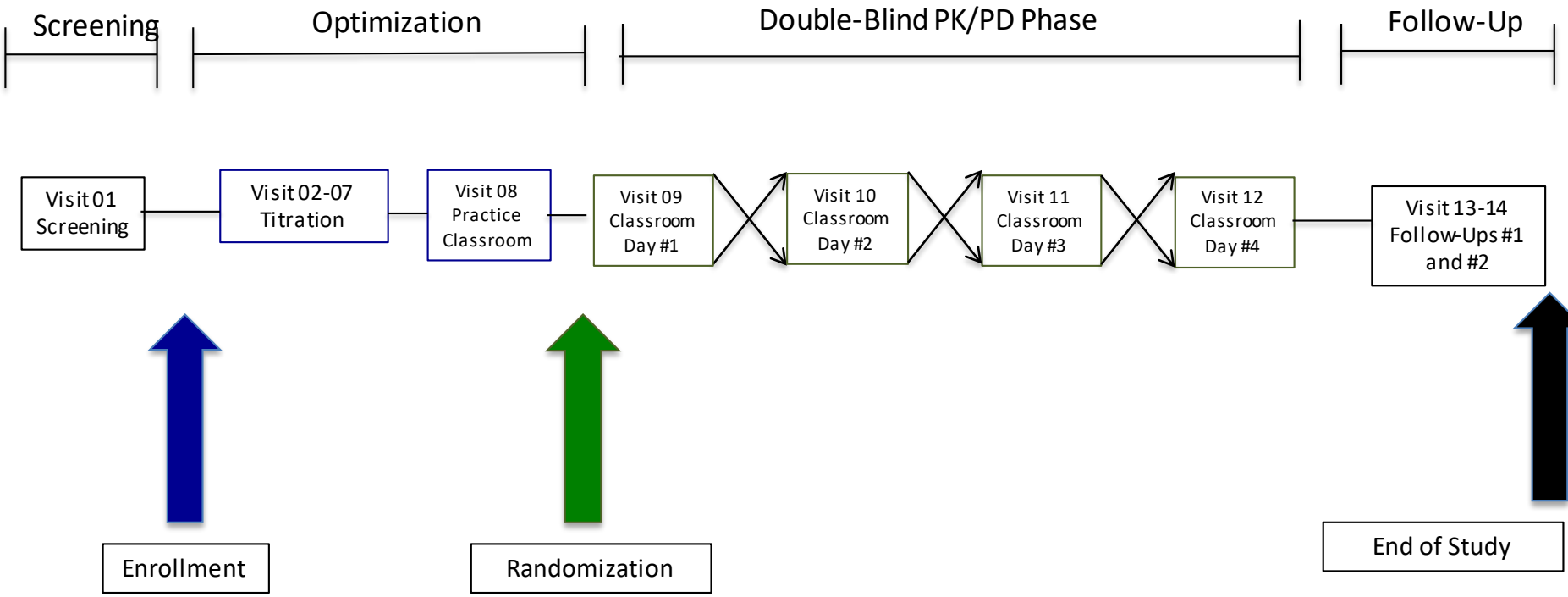
We measured hour by hour efficacy with standardized measures of observed behavior (SKAMP) as well as academic (mathematic) efficiency and accuracy (PERMP).

We hypothesized that PD measures will be similar at onset and offset in the two similarly designed OROS-like extended release MPH formulations (OROS MPH and Mallinckrodt generic equivalent) when contrasted to those of a comparator with a different PK profile (Quillivant XR).

Inclusion Criteria

- Male and female outpatients
- Ages 6-12 years at time of screening
- Diagnosis of DSM-5 ADHD combined, predominantly inattentive or hyperactive/impulsive presentation
- ≥ 90th percentile normative value for gender and age on the ADHD RS-IV total score at screening or baseline

PKPD Studies of MPH ER Products in Pediatric ADHD Patients



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Optimization.

The study design included an initial open-label (OL) treatment with OROS MPH for 4 to 6 weeks for dose optimization. The starting dose of the OL phase was 18 mg of OROS MPH for all study participants, which was titrated at weekly intervals at 18 mg increments until an optimal dose was achieved or a maximum of 72 mg per day was reached.

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Optimized subjects were enrolled in the double-blind (DB) phase of the study. Subjects were randomly assigned to one of 24 different treatment sequences over 4 weeks.

The DB phase consisted of four weekly periods with each consisting of blinded treatment with one of the four medication treatments (OROS-MPH, Mallinckrodt MPH ER, Quillivant or Placebo).

On the last day of each period (Saturday), subjects were evaluated in a laboratory classroom setting.

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Statistical Analysis

During the optimization phase, the optimal individual dose for the randomized treatment phase was selected as the dose associated with at least a 30% improvement on the ADHD-RS-IV score. Due to this specific study design, different individual doses selected for the treatment phase providing similar clinical response.

Therefore, the statistical comparison of the longitudinal scores (SKAMP-Total and PERMP-Corrected) was conducted by comparing the data on the placebo arm with the pooled data in each treatment arm for Concerta, Quillivant XR, and Mallinckrodt ER.

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Statistical Analysis

The primary efficacy measures were the change from baseline in the SKAMP-total and in the PERMP-Corrected score. These variables were analyzed using a Mixed effect Model Repeat Measurement (MMRM) analysis. The model included terms for treatment, time, baseline, treatment by time interaction and baseline by week interaction. The random effects were specified using the repeated statement to account for serial within-subject correlation.

A significance level of $\alpha = 0.05$ was used to establish the significance of treatment effect, which was determined using the mixed effect model adjusted means (LSMEANS). The LSMEANS statement computed the least squares means (LS-means) of fixed effects. The comparisons among treatment accounted for the multiple comparison adjustment using the Tukey method.

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Participant Flow Chart

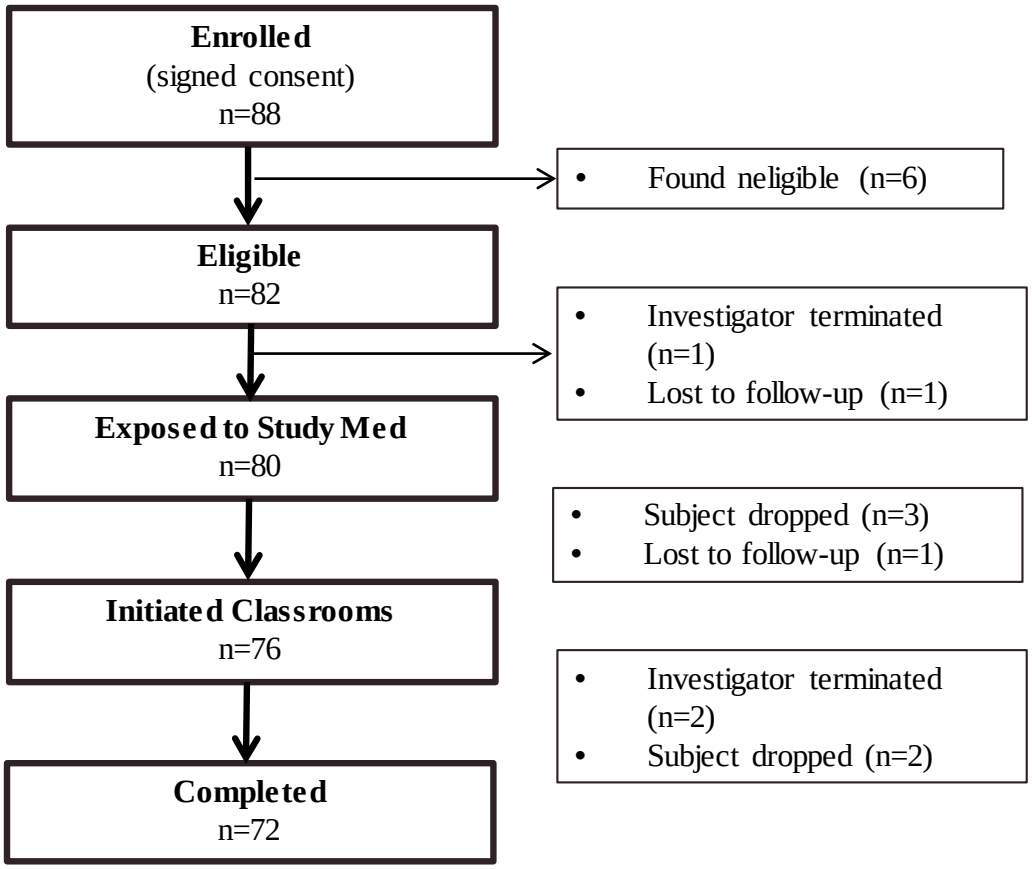

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Table 1. Demographic characteristics of sample

Characteristic	Total Exposed N=80
	Mean ± SD
Age	9.5 ± 1.8
	N (%)
Male	59 (73.75)
Race	
Asian	2 (2.5)
Black/African American	14 (17.5)
Caucasian	45 (56.25)
More than one	16 (20.0)
Unknown/Not reported	3 (3.75)

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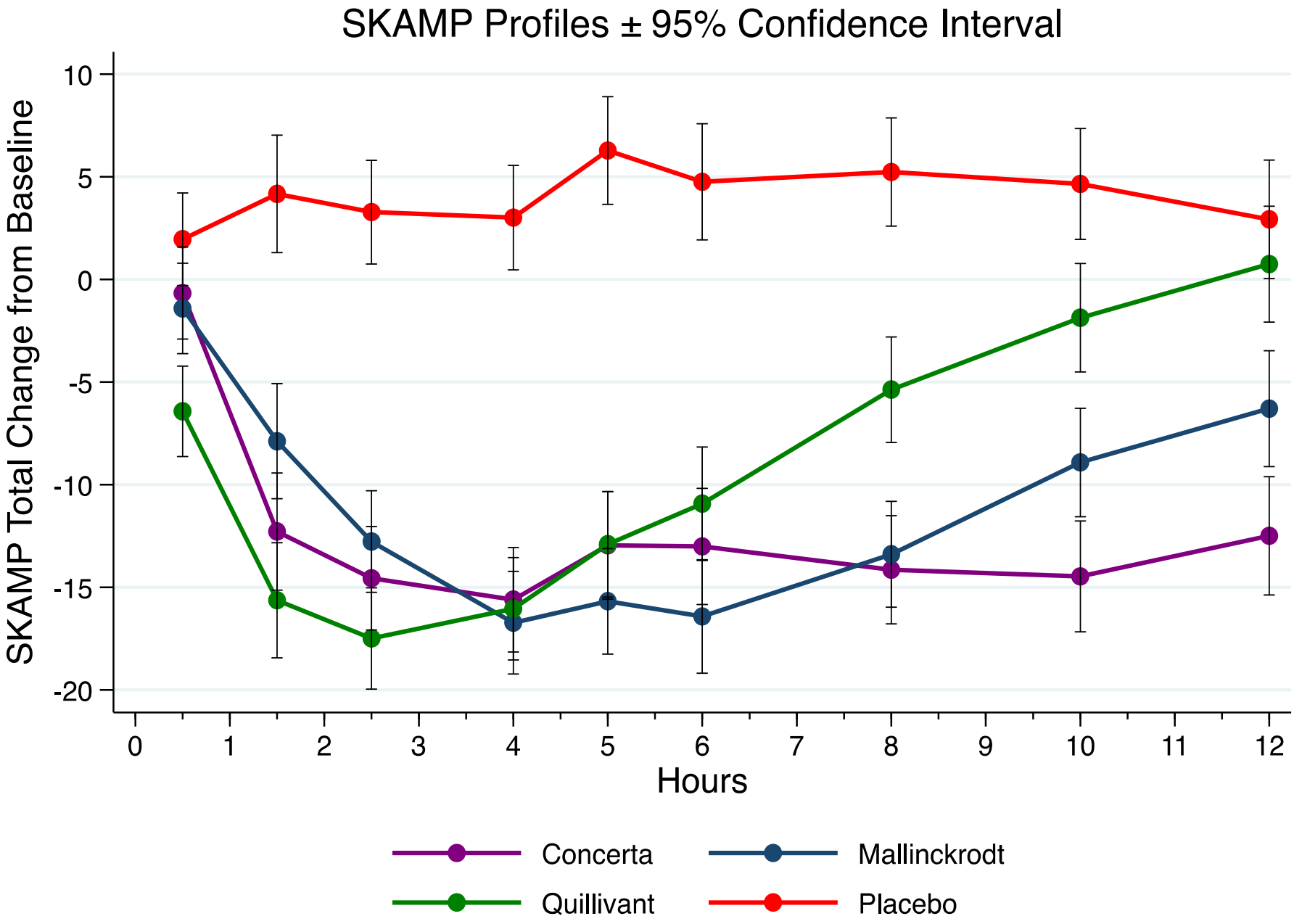
Behavioral Observations (SKAMP-TOTAL)

There was a rapid response of behavioral symptoms as assessed through the SKAMP for all three long-acting MPH formulations with peak response across formulations between 2 ½ to 4 hours post dosing that was sustained to 6 hours post dosing.

After hour 6, the behavioral response to Quillivant XR waned, the response to Concerta persisted and the response to Mallinckrodt ER was intermediate.

Of note, behavioral symptoms associated with the placebo condition remain even across the day up to the last measurement at 12 hours


SKAMP Profiles ± 95% Confidence Interval
SKAMP Total Change from Baseline
10
5
0
-5
-10
-15
-20
0
1
2
3
4
5
6
7
8
9
10
11
12
Hours
Concerta
Mallinckrodt
Quillivant
Placebo

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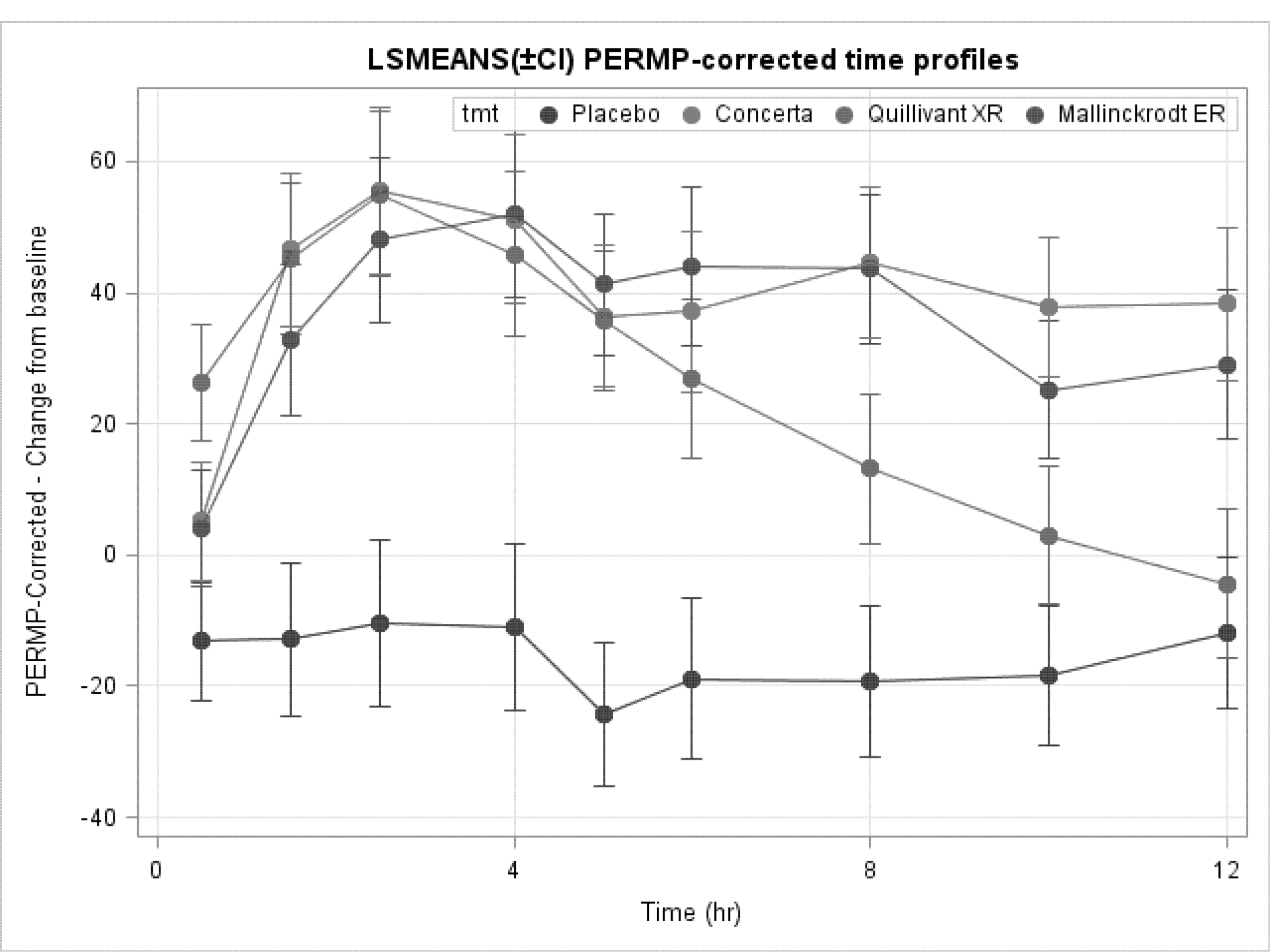
Academic (Mathematic) Efficiency and Accuracy (PERMP-Corrected scores)

Consistent with the behavioral measures, there was a rapid response of PERMP scores for all three long-acting MPH formulations with peak response between measurements at 2 ½ to 4 hours post dosing that was sustained up to 6 hours post dosing.

After hour 6, the academic response to Quillivant XR waned, the response to Concerta persisted and the response to Mallinckrodt ER was intermediate.

Like for the behavioral measure, the response associated with the placebo condition remained even across the day up to the last measurement at 12 hours.


LSMEANS(±CI) PERMP-corrected time profiles
tmt
Placebo
Concerta
Quillivant XR
Mallinckrodt ER
PERMP-Corrected - Change from baseline
60
40
20
0
-20
-40
0
4
8
12
Time (hr)

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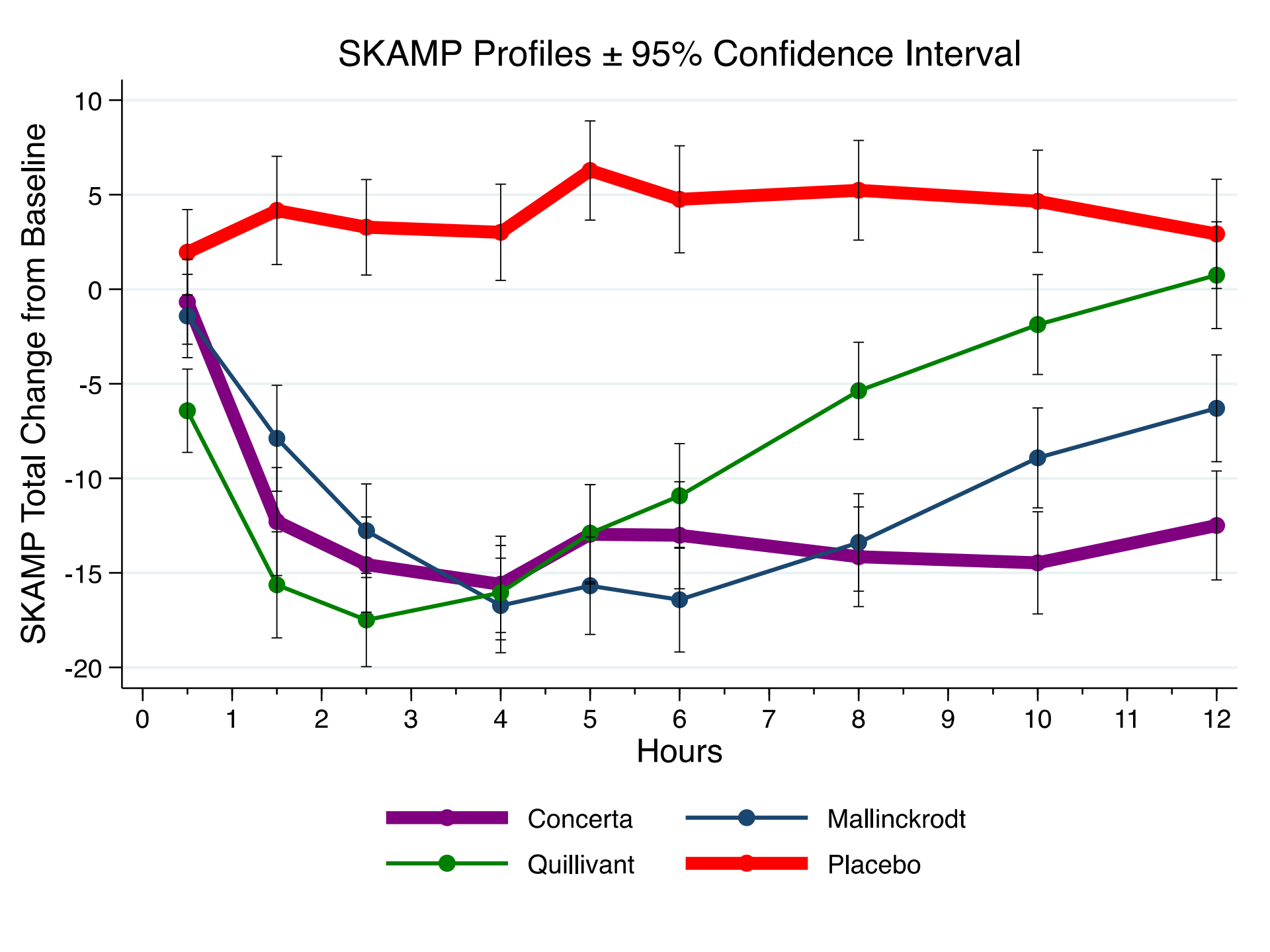
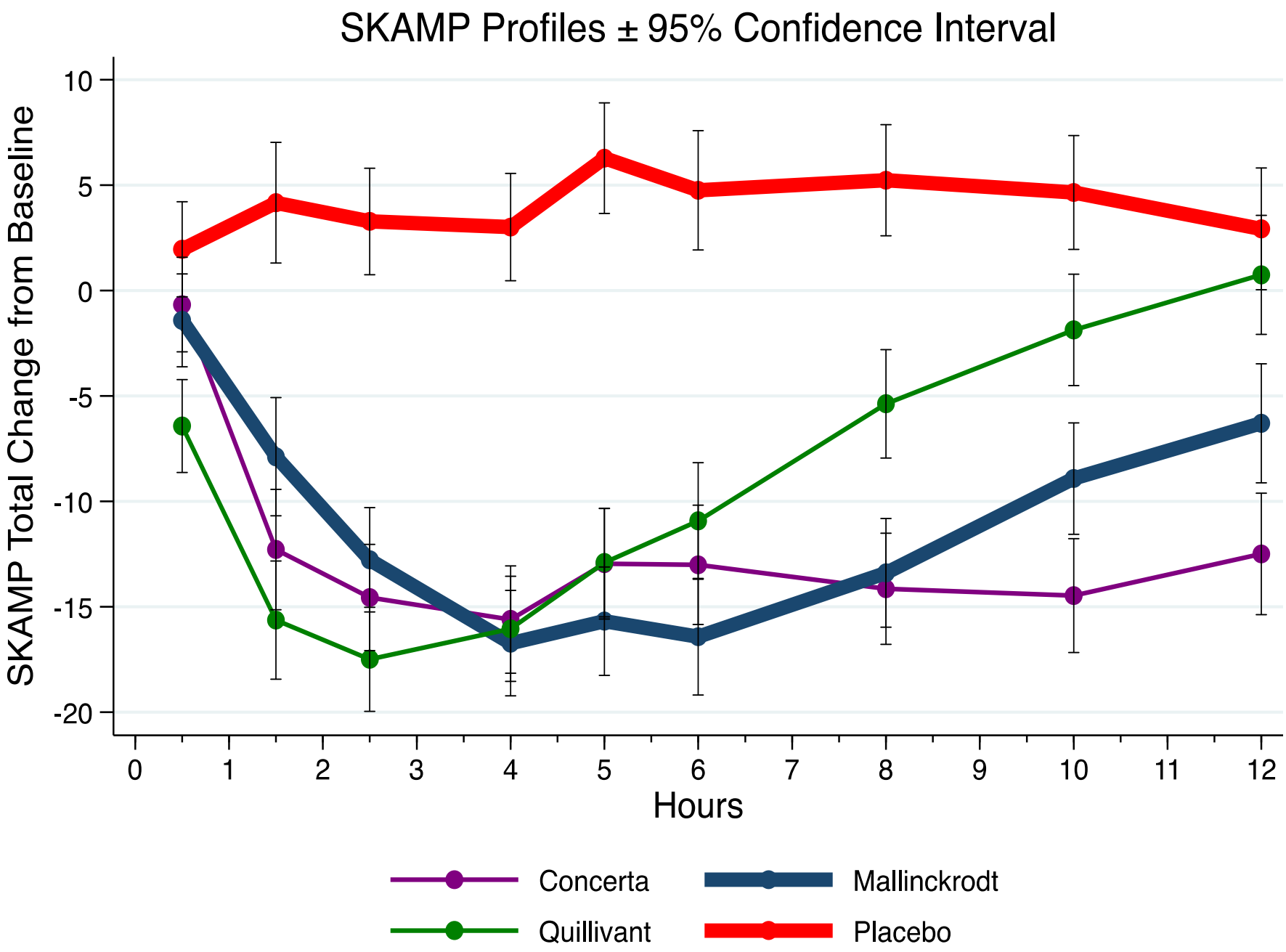
Concerta and Mallinckrodt ER had a comparable statistically significant effect vs. placebo, on both measurements (SKAMP, PERMP) from 1.5 hour up to 12 hours post-dose.

Concerta and Mallinckrodt ER were not statistically different from each other on either measurement (SKAMP, PERMP) across the day.


SKAMP Profiles ± 95% Confidence Interval
SKAMP Total Change from Baseline
10
5
0
-5
-10
-15
-20
0
1
2
3
4
5
6
7
8
9
10
11
12
Hours
Concerta
Mallinckrodt
Quillivant
Placebo


SKAMP Profiles ± 95% Confidence Interval
SKAMP Total Change from Baseline
10
5
0
-5
-10
-15
-20
0
1
2
3
4
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11
12
Hours
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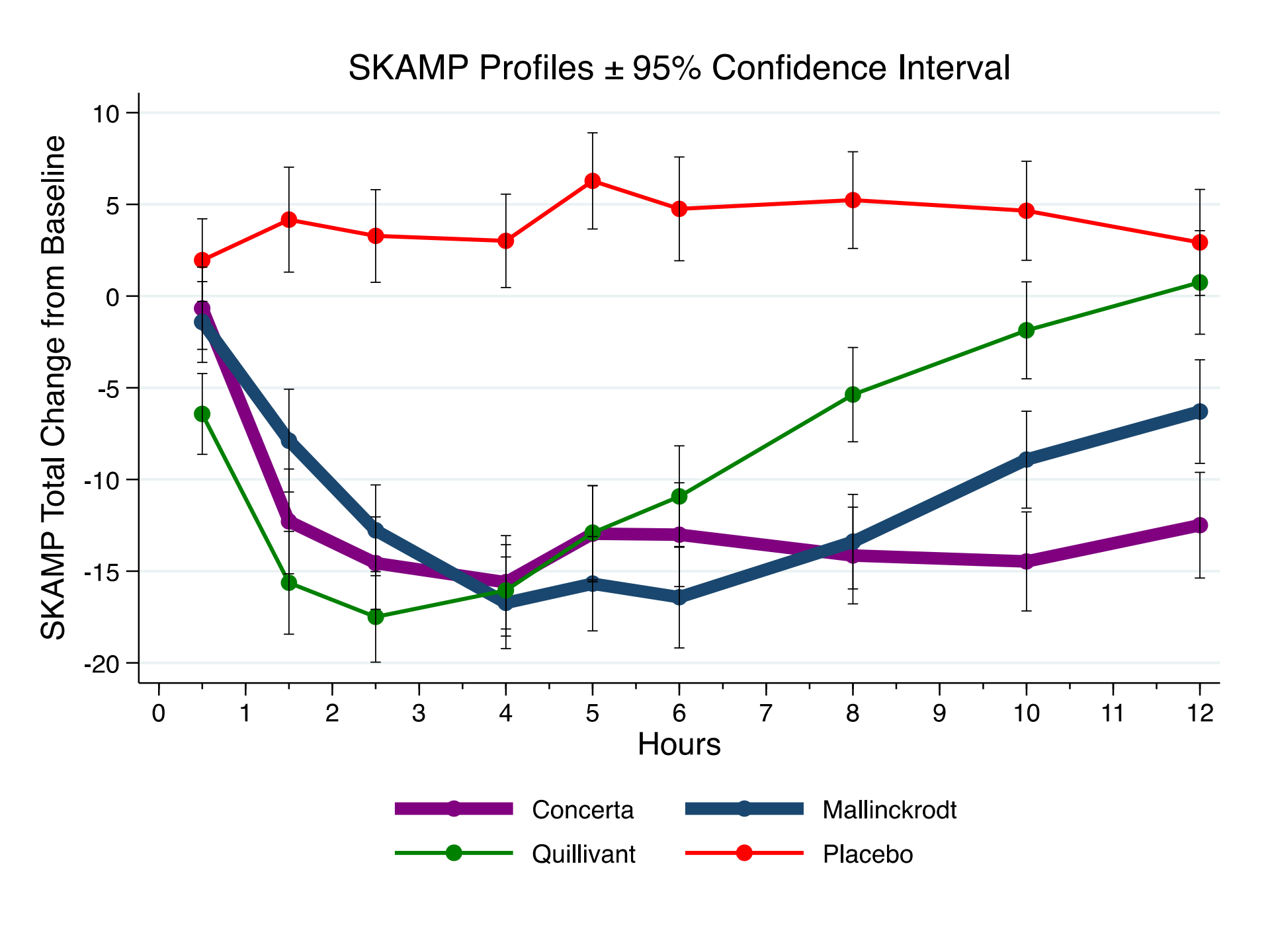
SKAMP Profiles ± 95% Confidence Interval
SKAMP Total Change from Baseline
10
5
0
-5
-10
-15
-20
0
1
2
3
4
5
6
7
8
9
10
11
12
Hours
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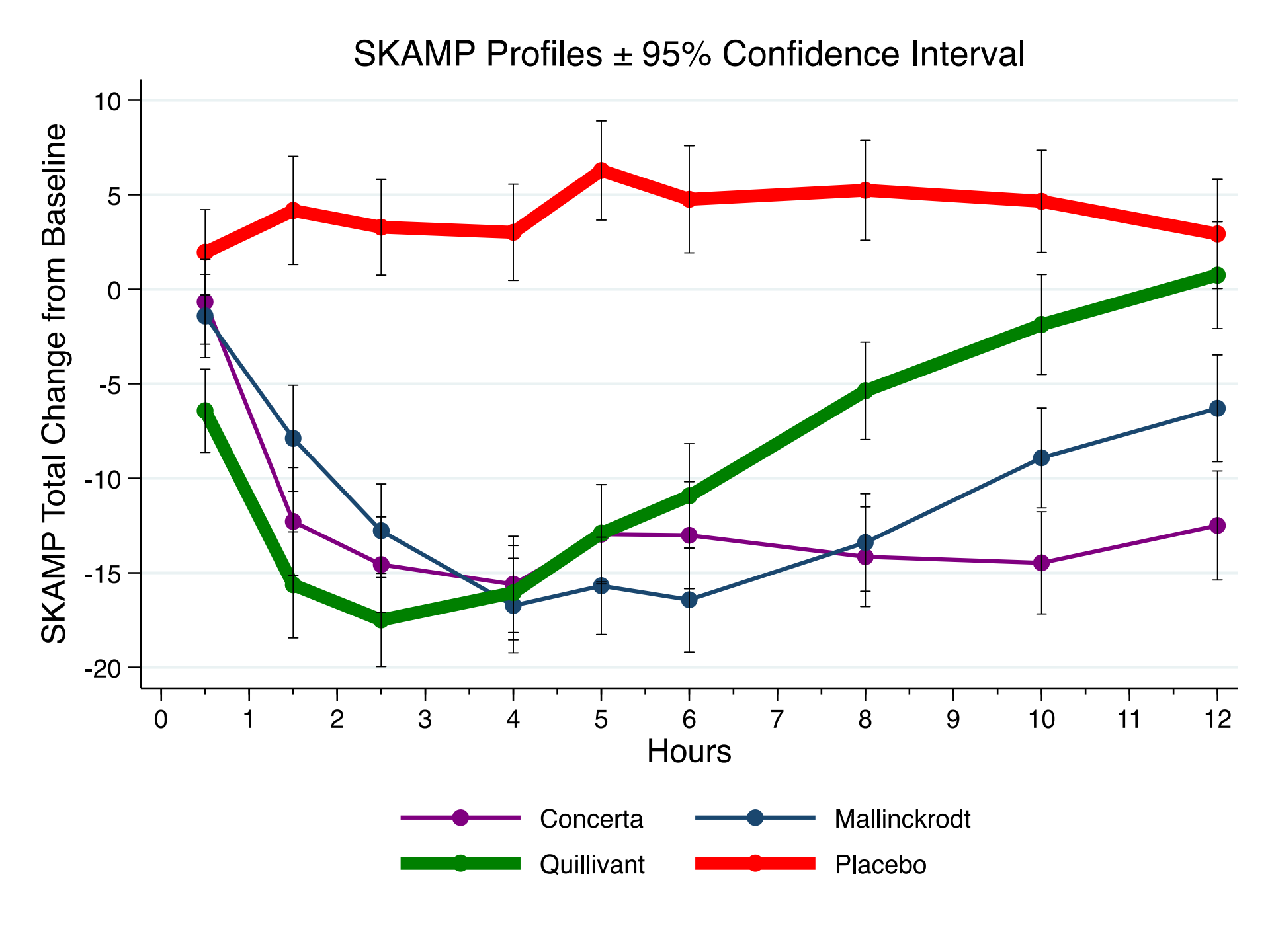
In contrast, while Quillivant XR showed a statistical improvement with respect to placebo starting at 0.5 hours post dose and lasted up to 8 hours post-dose on both measurements (SKAMP, PERMP), it was statistically inferior to both Concerta and Mallinckrodt ER on both measurements (SKAMP, PERMP) after hour 8 post dosing.

Moreover, Quillivant XR was statistically *inferior* to Concerta on the SKAMP from 8 to 12 hours post dose and on the PERMP from 10 to 12 hours post dose.

Quillivant XR was also statistically inferior to Mallinckrodt ER on the SKAMP at 8 hours and on the PERMP at 12 hours


SKAMP Profiles ± 95% Confidence Interval
SKAMP Total Change from Baseline
10
5
0
-5
-10
-15
-20
0
1
2
3
4
5
6
7
8
9
10
11
12
Hours
Concerta
Mallinckrodt
Quillivant
Placebo

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The similarities in hour by hour PD findings between Concerta and Mallinckrodt generic) across the entire day in both standardized measures of observed behavior (SKAMP) as well as objective measures of academic (mathematic) efficiency and accuracy (PERMP) support the robustness of the findings.

These results are not surprising since both compounds were designed to release with the same ascending PK profile and intended duration (12 hours).

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Our findings also confirmed our study hypothesis, that PD measures of a Concerta-like profile would be different when contrasted to those of a comparator with a different PK profile (Quillivant).

The Concerta PK profile is an ascending curve whereas the Quillivant XR release is more rapid, early release, though both have a similar intended duration of effect (12 hrs).

The response to Quillivant XR was similar to the other two formulations up through 6 hours. Compared to Concerta, the treatment effect of Quillivant XR was substantially reduced from 8 or 10 hours to 12 hours post-dose. These results are not surprising since these compounds were designed to have a different PK profile.

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Our findings should be viewed in light of some limitations.

Our findings of the duration of PD effect in Quillivant are inconsistent with a precious study in which the PD effect was of longer duration.

We don't know why the results are inconsistent. One possibility is that, in this study, we optimized response to Concerta. It is possible that the optimal dose for Concerta is not the correct optimal dose for Quillivant. Future studies should investigate comparisons between drugs with the OROS MPH profile and Quillivant in subjects optimized to Quillivant.

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Despite these limitations, in this controlled study, PD effects for differing MPH ER formulations confirmed our study hypothesis.

For the two compounds designed to have a similar PK profile and intended duration of action (Concerta and Mallinckrodt generic) PD effects were similar across the day.

In contrast, for the compound with a different PK profile but same intended duration (Quillivant), the PD measures were less robust than Concerta in later hours.

If confirmed, these findings contribute the methodology of evaluating bioequivalence in MPH ER formulations.