Cognitive Assessment After Multiple Ascending Doses of TAK-935 (OV935) in Healthy Subjects

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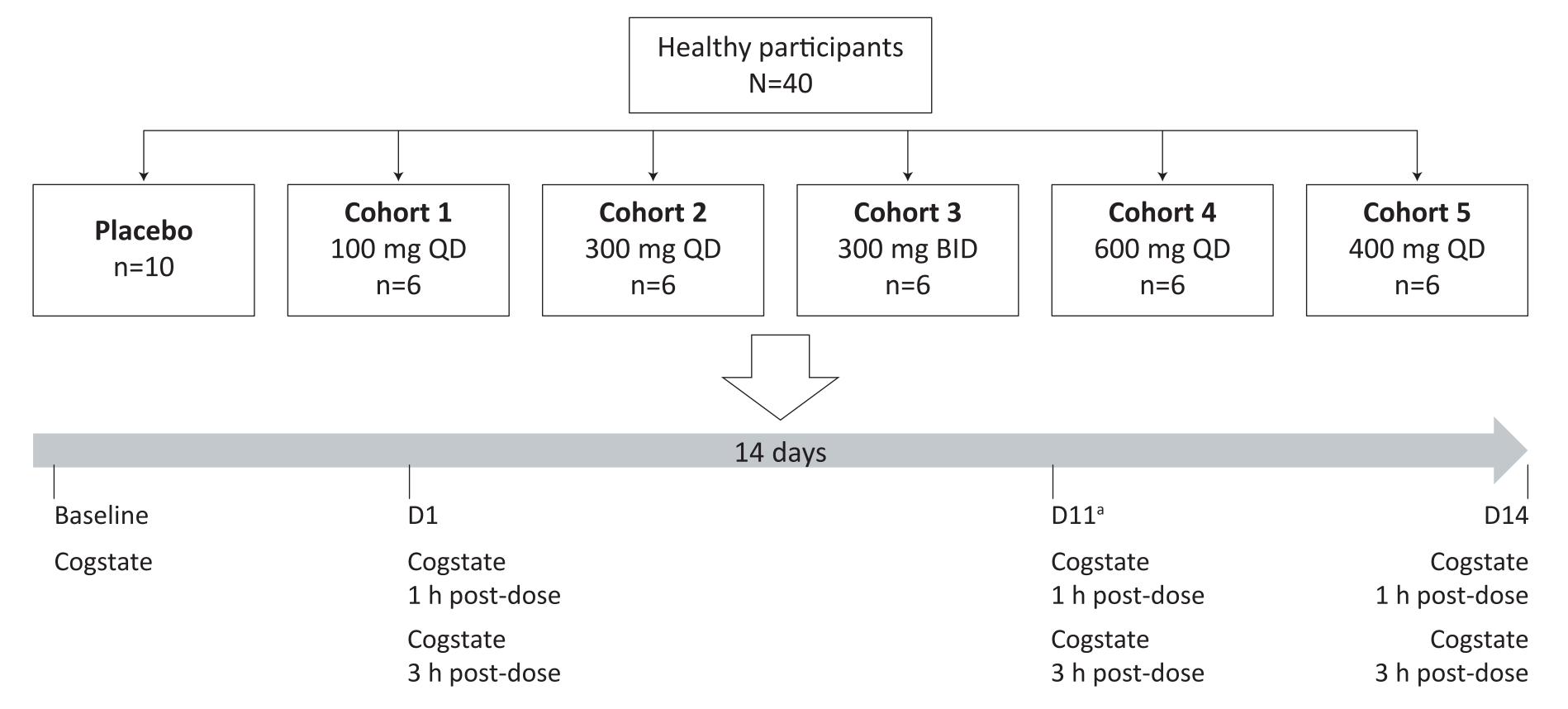
Introduction

- TAK-935 is a potent and selective inhibitor of the cholesterol 24-hydroxylase (CH24H) enzyme.
- CH24H converts brain cholesterol to 24S-hydroxycholesterol (24HC), a positive allosteric modulator at the N-methyl-D-aspartate
- 24HC can drive glutamatergic overactivation by modulation via NMDA channel activity, which implies a potential role in central nervous system diseases, such as epilepsy.
- TAK-935 is currently under development for the treatment of rare epilepsies.
- In a murine epilepsy model (a pentylenetetrazol-induced mouse kindling model), TAK-935 delayed seizure onset and severity in a dose-dependent manner.
- The present study was a phase 1 randomized trial of multiple rising doses (MRD) of TAK-935 in healthy subjects. The main findings of this study have been previously presented.¹
- TAK-935 was well tolerated in doses up to 400 mg QD, and the pharmacokinetic and pharmacodynamic profile was acceptable and warranted further study.1
- Considering that antiepileptic drugs may have a negative impact on cognition,² this study of TAK-935 in healthy subjects also evaluated the effect on cognition using tests from the Cogstate Battery (Table 1). This poster reports the results from that evaluation.

Methods

• This was a phase 1, randomized, double-blind, placebo-controlled study that enrolled 40 healthy subjects (Figure 1).

Figure 1. Trial Schema and Randomization



^aAssessments on day 11 were only done for 2 cohorts: cohort 3, 300 mg BID, and cohort 4, 600 mg QD, which were discontinued early. BID, twice daily; D, day; h, hour; QD, daily.

Table 1. Components of Cogstate Battery

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Aspect of Cognitive Function	Cogstate Battery	Primary Measure
Executive function	Groton Maze Learning Test	Speed of performance
Learning	One Card Learning Test	Accuracy of performance
Psychomotor	Detection Test	Speed of performance
Attention	Identification Test	Speed of performance
Working memory	One Back Test	Accuracy of performance

- The Cogstate Battery takes approximately 20 minutes to complete and was administered via a standard computer system.³
- For each cognitive test, mean value and standard deviation (SD) of performance were computed at baseline for all participants. Individual post-baseline assessments were standardized calculating their difference from the baseline group mean and dividing it by the baseline group SD.
- Group mean standardized changes from baseline scores were then computed for each treatment cohort and placebo.
- All scores were converted to Z scores, and scores within a range of -1 and +1 plus were not considered significant.
- A group mean standardized change from baseline of ≤-1 was classified as a clinically important cognitive decline.

Study Subjects

• The majority of subjects were white (31 subjects [77.5%]), and half or more of subjects in each dose group were male. Mean age ranged from 26.7 to 40.3 years.¹

Effects of TAK-935 on Cognition

Figure 2. Executive Function (Groton Maze Learning Test)

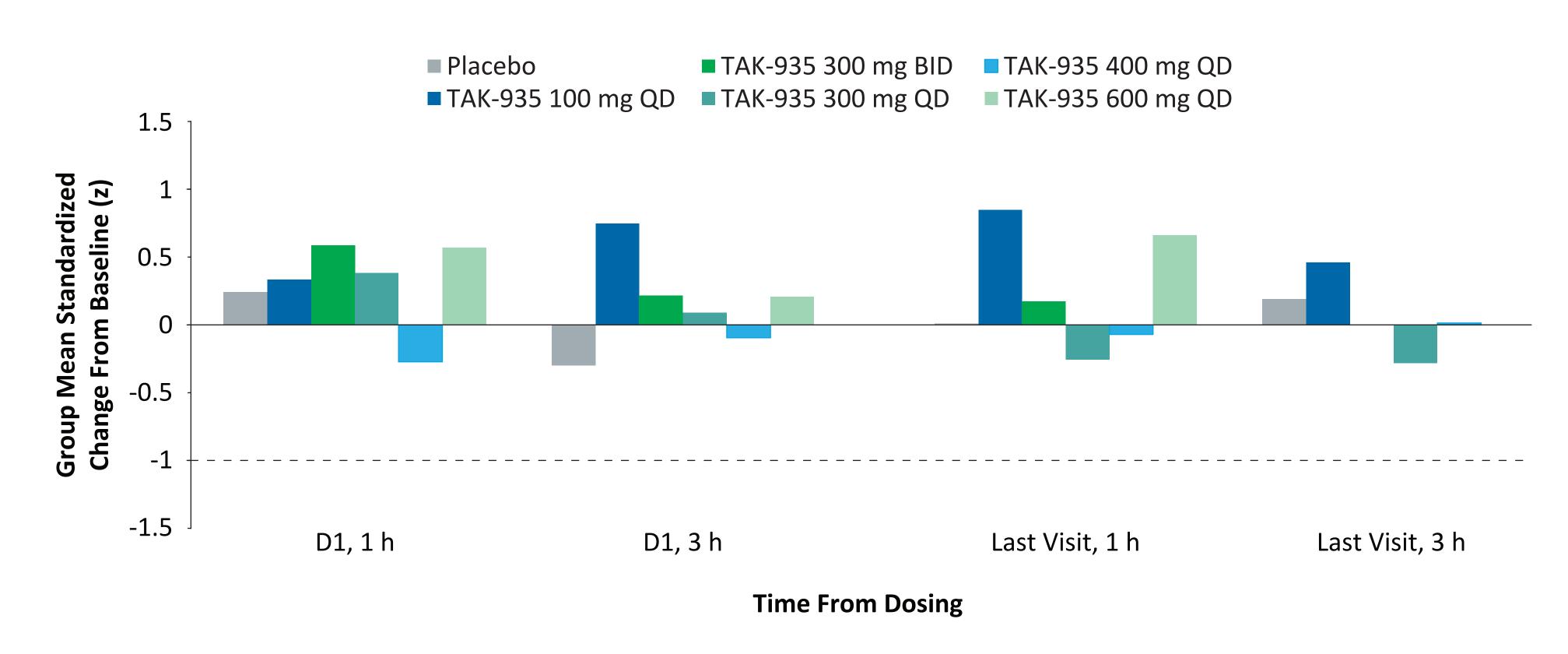


Figure 3. Learning (One Card Learning Test)

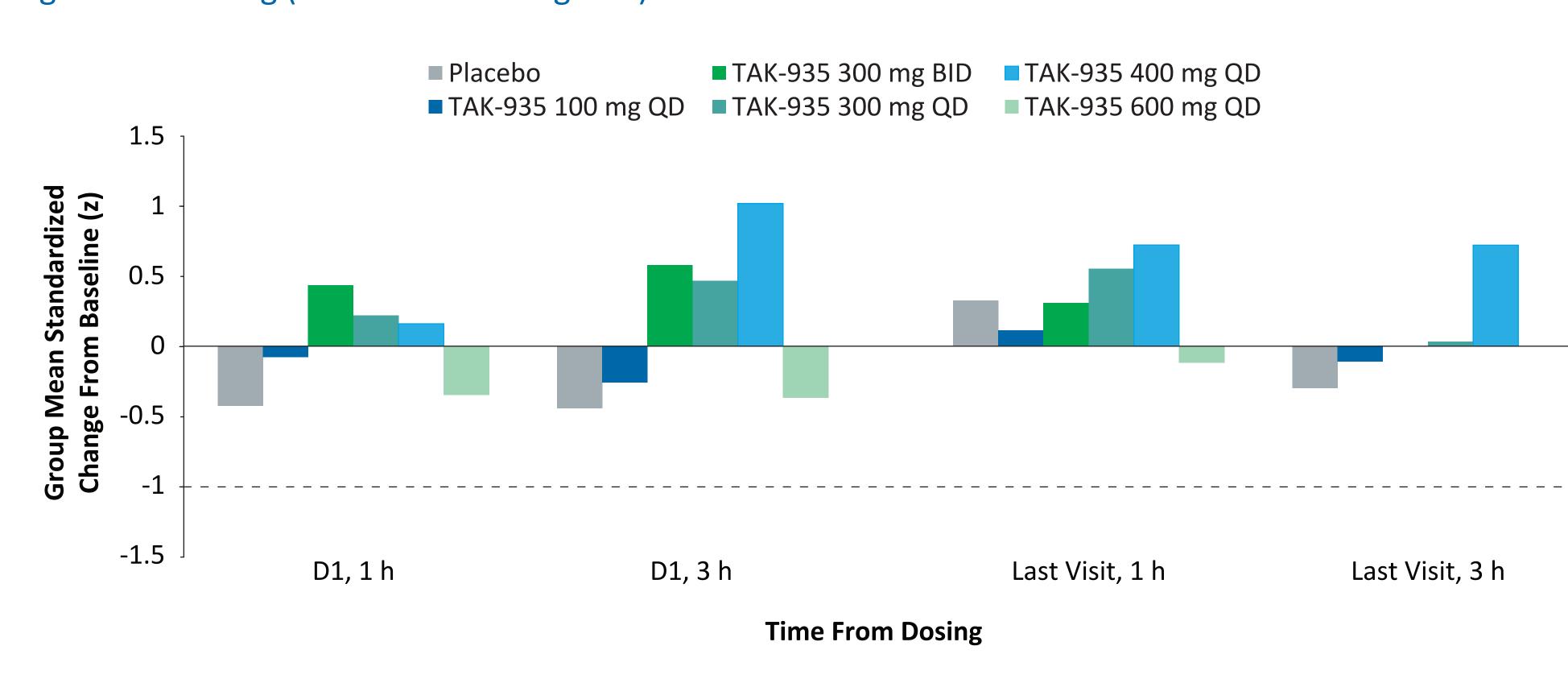


Figure 4. Psychomotor Function (Detection Test^a)

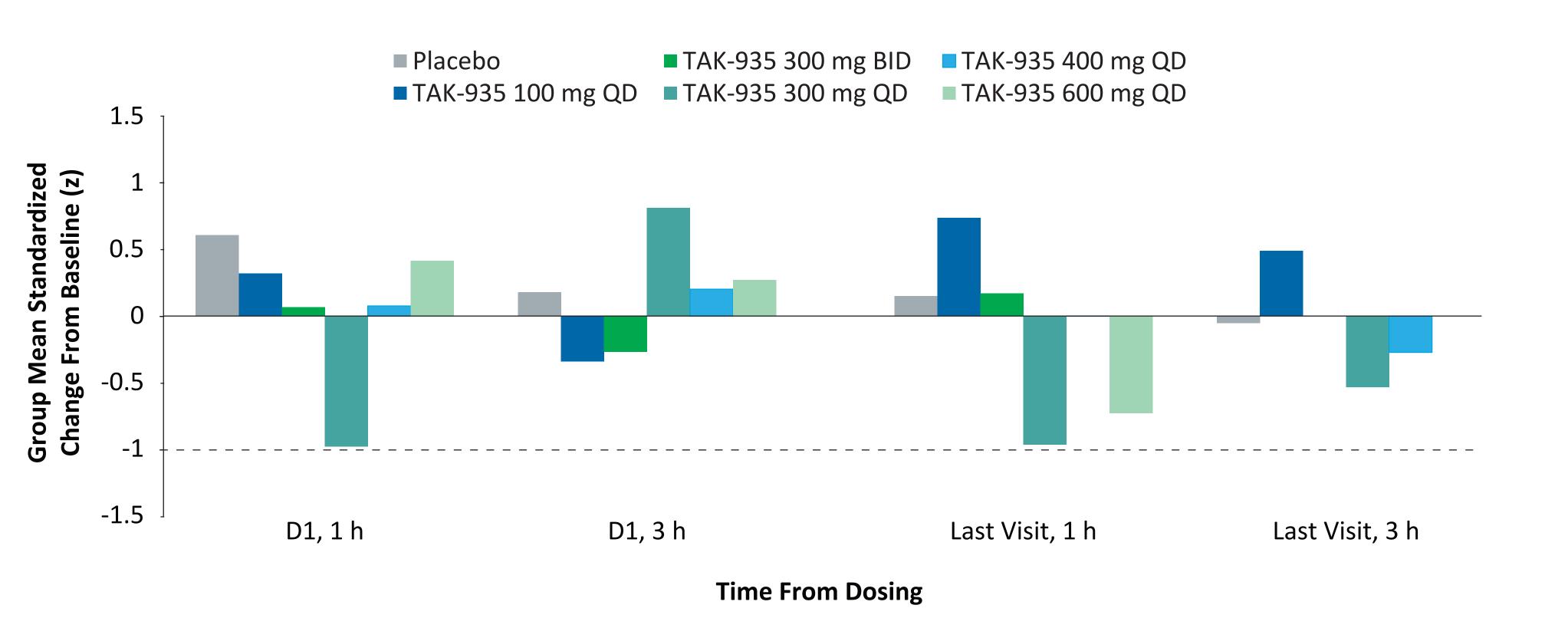
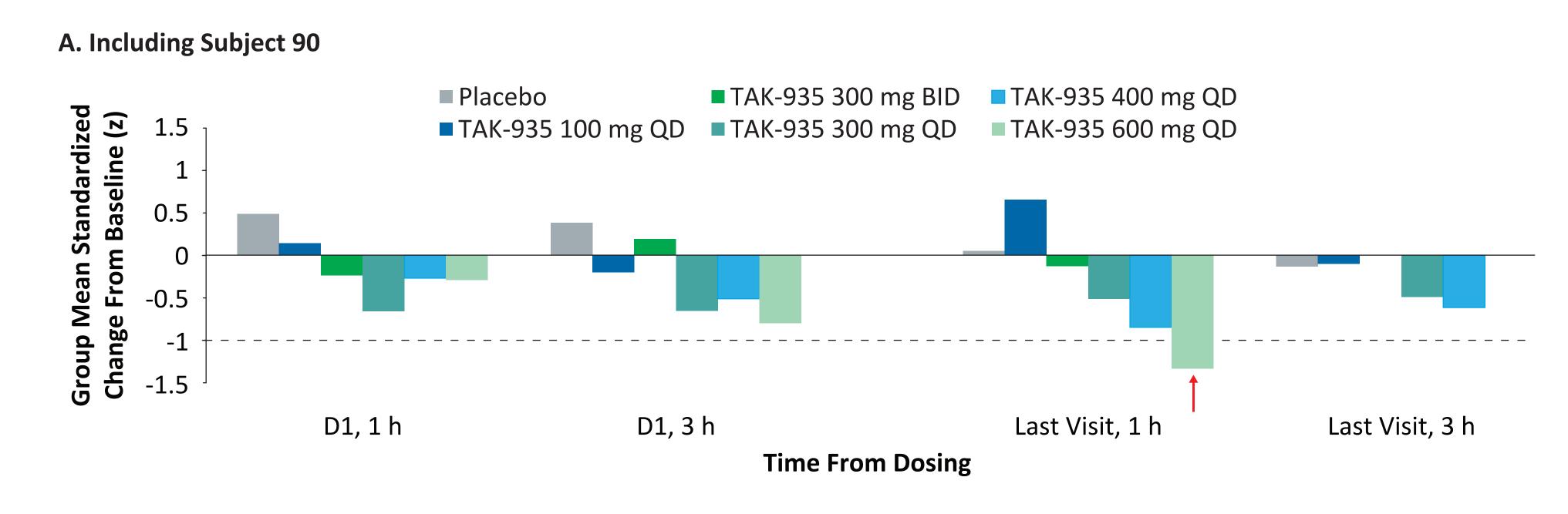


Figure 5. Attention (Identification Test^b)



B. Excluding Subject 90

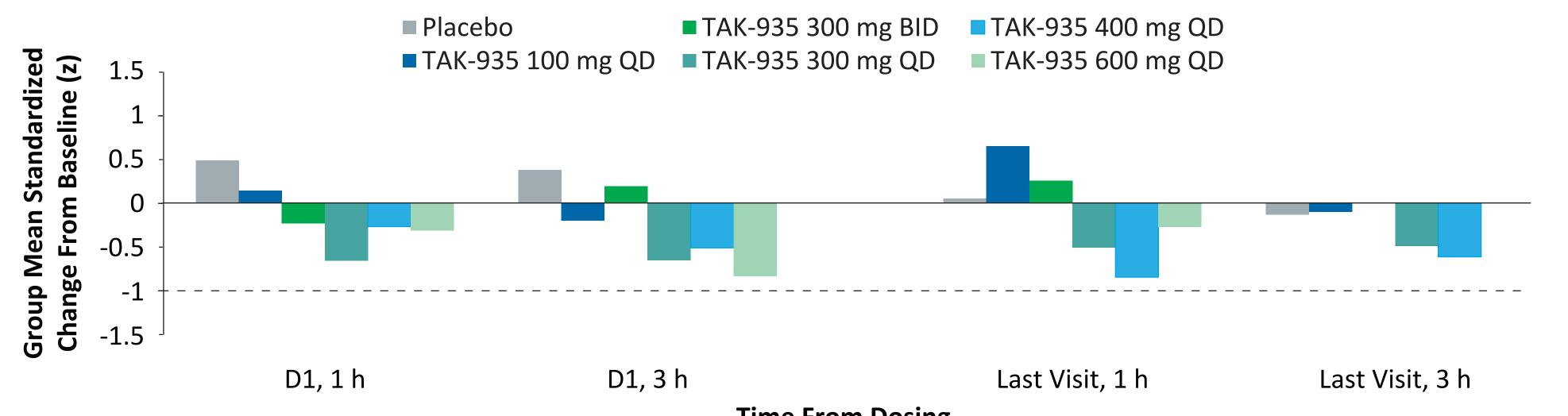
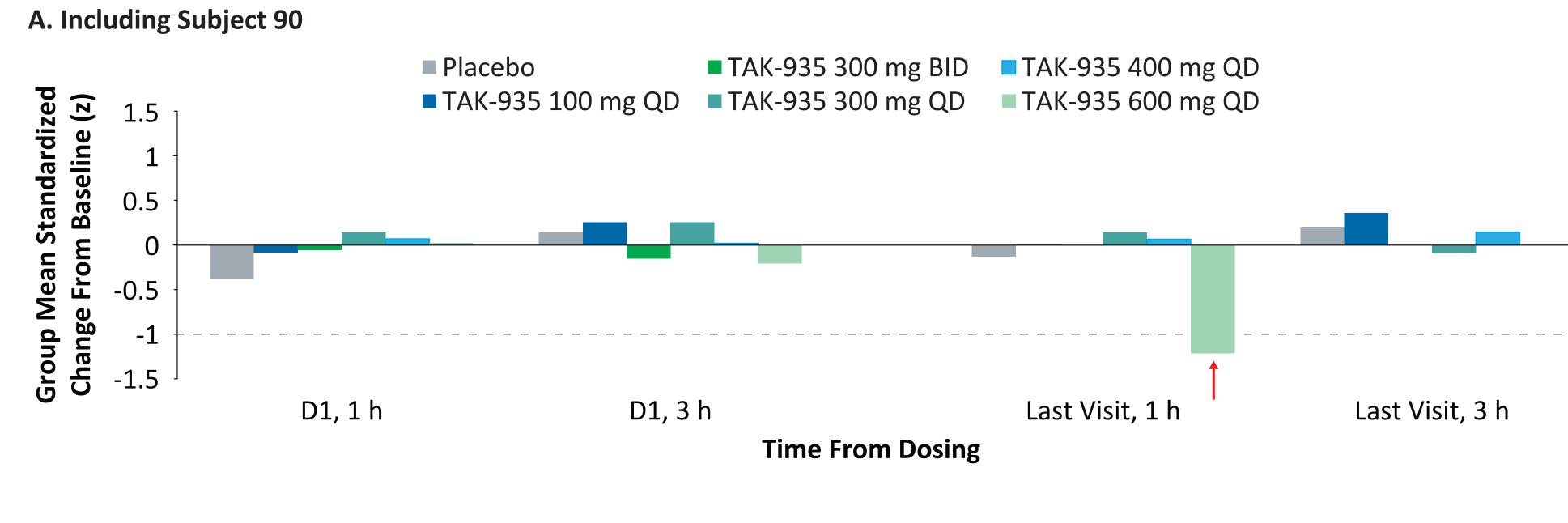
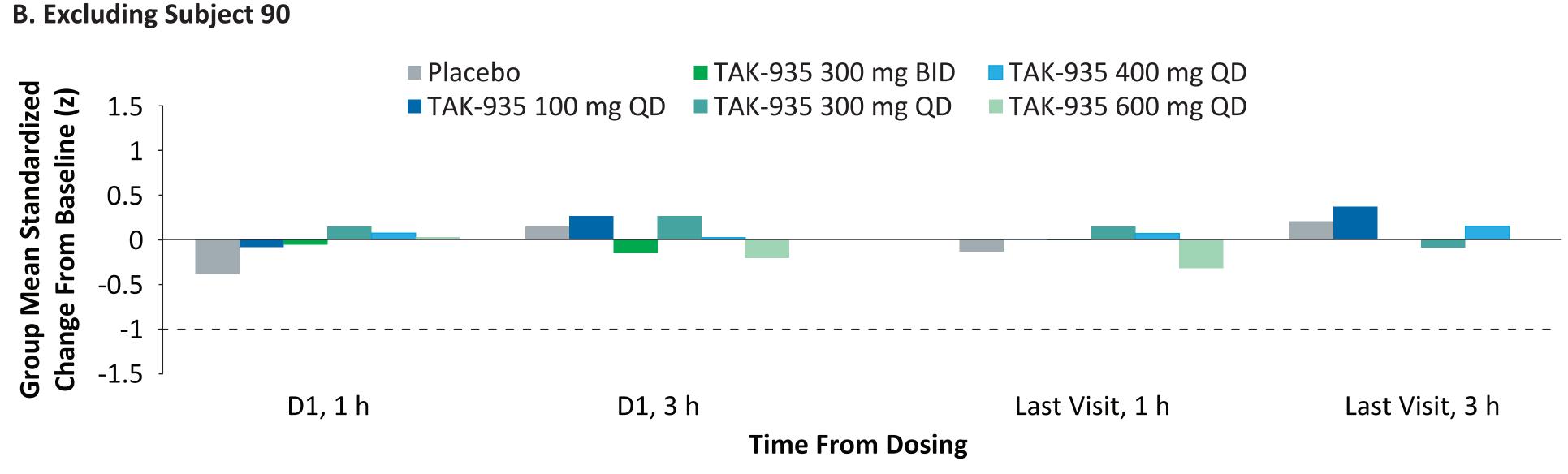


Figure 6. Working Memory (One Back Test)





Negative signs indicate decline from baseline. Dashed line represent a group mean standardized change from baseline of <-1, which was classified as a clinically important cognitive decline. Red arrow represents clinically important decline (ie, standard change from baseline) 3-hour data were not collected in 600-mg QD and 300-mg BID cohorts due to an oversight at study site. ^aSimple reaction time. ^bChoice reaction time. BID, twice daily; D, day; h, hours; QD, daily.

- Group mean standardized change from baseline is shown for each cognitive test on Figures 2 through 6. The graphs present change from baseline standardized Z scores by cohort. Changes within a range of -1 and +1 were not considered significant.
- Cognitive performance was generally comparable to placebo across all assessments for each of the cognitive tests for the 100-, 300-, and 400-mg QD and 300-mg BID cohorts. This indicates that for these cohorts, there was no evidence of cognitive decline post-dose (Figures 2-6).
- There was no evidence of cognitive decline post-dose on measures of executive function, learning, and psychomotor speed (Figures 2-4).
- In previous analyses, a subject in 600-mg QD dose arm was reported to have developed psychosis and his symptoms were ongoing during the cognitive tests. To determine the extent to which performance on cognitive tests in this participant could influence estimates of group mean standardized change from baseline, cognitive data for this subject was removed and group mean standardized change from baseline scores recomputed (Figure 5B and 6B).
- With data for the participant with psychosis removed, group mean standardized change from baseline in the 600-mg QD treatment group became comparable to the placebo group (Figures 5A and 6A).
- Upon exclusion of the subject, there were no significant declines across all assessments for each of the cognitive tests (Figures 5B

Summary and Conclusions

- TAK-935 (OV935) is a selective cholesterol 24-hydroxylase inhibitor under development for the treatment of rare epilepsies.
- This phase 1 MRD study investigated safety, pharmacokinetics, and pharmacodynamics of TAK-935 in healthy participants (N=40). Potential effects of TAK-935 on cognition were studied using the Cogstate Battery, a set of tests validated for the assessment of cognition in clinical trials.
- No effects on psychomotor speed, learning, or executive function were observed at any dose of TAK-935.
- No effects on attention or working memory were observed for all doses of TAK-935 below 600 mg.
- Once the one subject with psychosis was removed from the analysis, no effects on attention or working memory were observed for 600 mg of TAK-935.
- TAK-935 is being dosed at up to 300 mg BID in an up-titrated manner in ongoing studies in rare epilepsies.

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M.A. and B.H. are Takeda employees. L.L. is an Ovid employee. P.M. is a Cogstate employee.

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