

Neuroendocrine and other pharmacodynamic (PD) effects of ALKS 7119

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Introduction

- ALKS 7119 is a 5-HT transporter antagonist ($K_i=0.035 \mu\text{M}$) and NMDA receptor antagonist ($K_i=7.44 \mu\text{M}$) and is therefore hypothesized to influence the levels of serotonin and glutamate in the brain.
- Serotonin and glutamate are involved in the pathophysiology of many neuropsychiatric disorders, for example in depression and schizophrenia.
- Central Nervous System (CNS) effects of ALKS 7119 were assessed by measuring serum cortisol and prolactin levels, and by the NeuroCart[®], a validated battery of drug sensitive CNS tests.

Methods

- First-in-human, double-blind, randomized, placebo-controlled, single ascending dose study.
- 10 cohorts of 10 healthy males received ALKS 7119 or placebo (ratio 8:2).
- Doses: 3, 10, 25, 50, 75, 100, 125, 150, 175, 200 mg.
- Plasma samples for PK and neuro-endocrine hormone were collected at pre-dose and at several post-dose time points until 36 hours post-dose.
- NeuroCart[®] assessments were repeatedly performed from pre-dose until 12 hours post-dose.

Results

- The pharmacokinetic (PK) profile was linear over the evaluated dose range.
- t_{max} : 0.5 - 4 hours, $t_{1/2}$: 7 - 9 hours.
- Significant dose-dependent increases at around t_{max} were observed for:
 - serum cortisol ($p=0.003$, figure 1)
 - serum prolactin ($p=0.001$, figure 2)
 - pupil/iris ratio left ($p<0.001$, figure 3)
 - pupil/iris ratio right ($p=0.002$, figure 4)

Conclusion

- The results indicate that ALKS 7119 has some penetration of the Blood Brain Barrier (BBB).
- Comparison of the CNS profile of ALKS 7119 with profiles of other known CNS active drugs indicates that ALKS 7119 is most comparable with inhibition of SERT receptors.

Figure 1. Mean (\pm Standard Error) Serum Concentrations of Cortisol over time

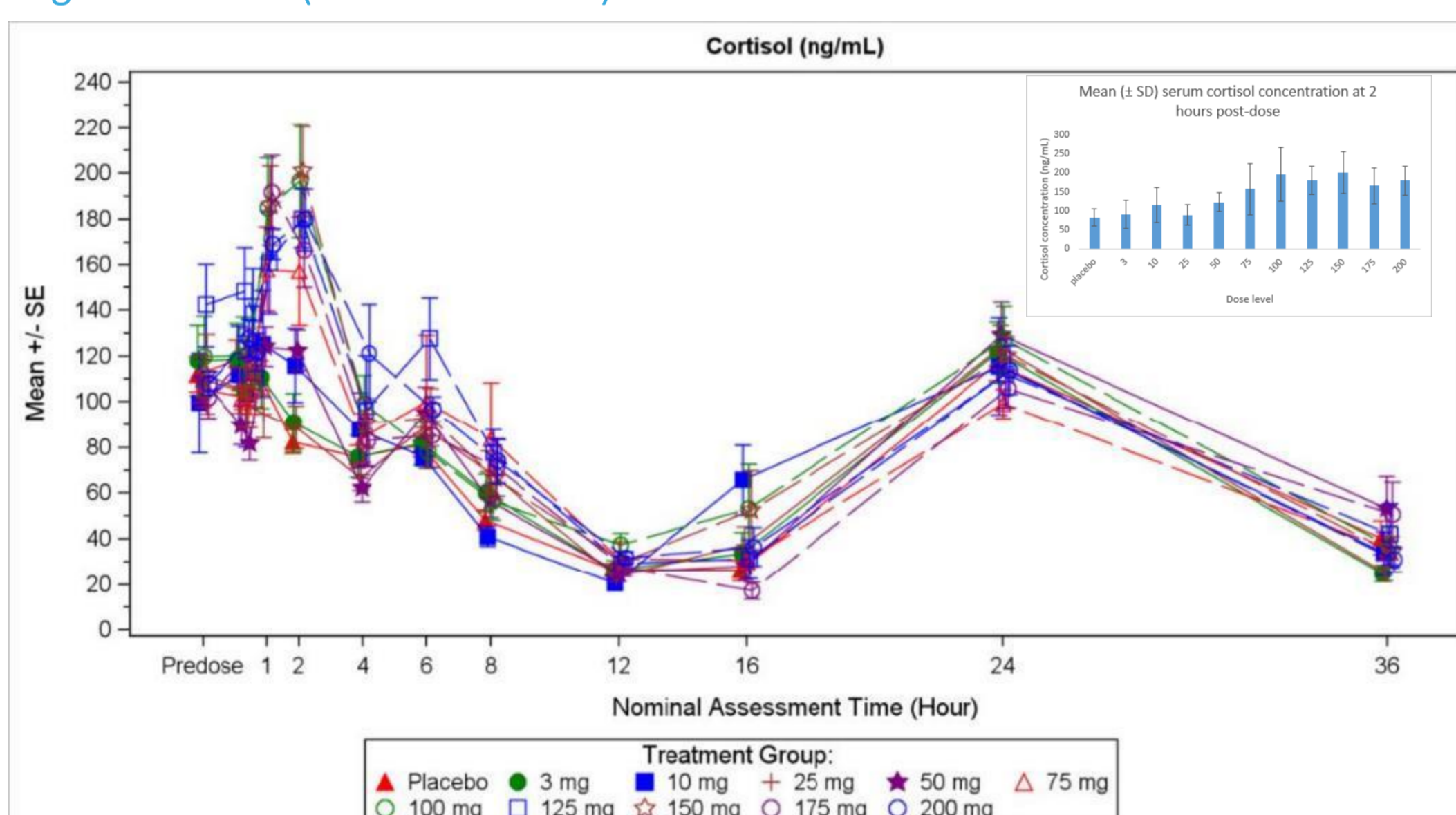


Figure 2. Mean (\pm Standard Error) Serum Concentrations of Prolactin over time

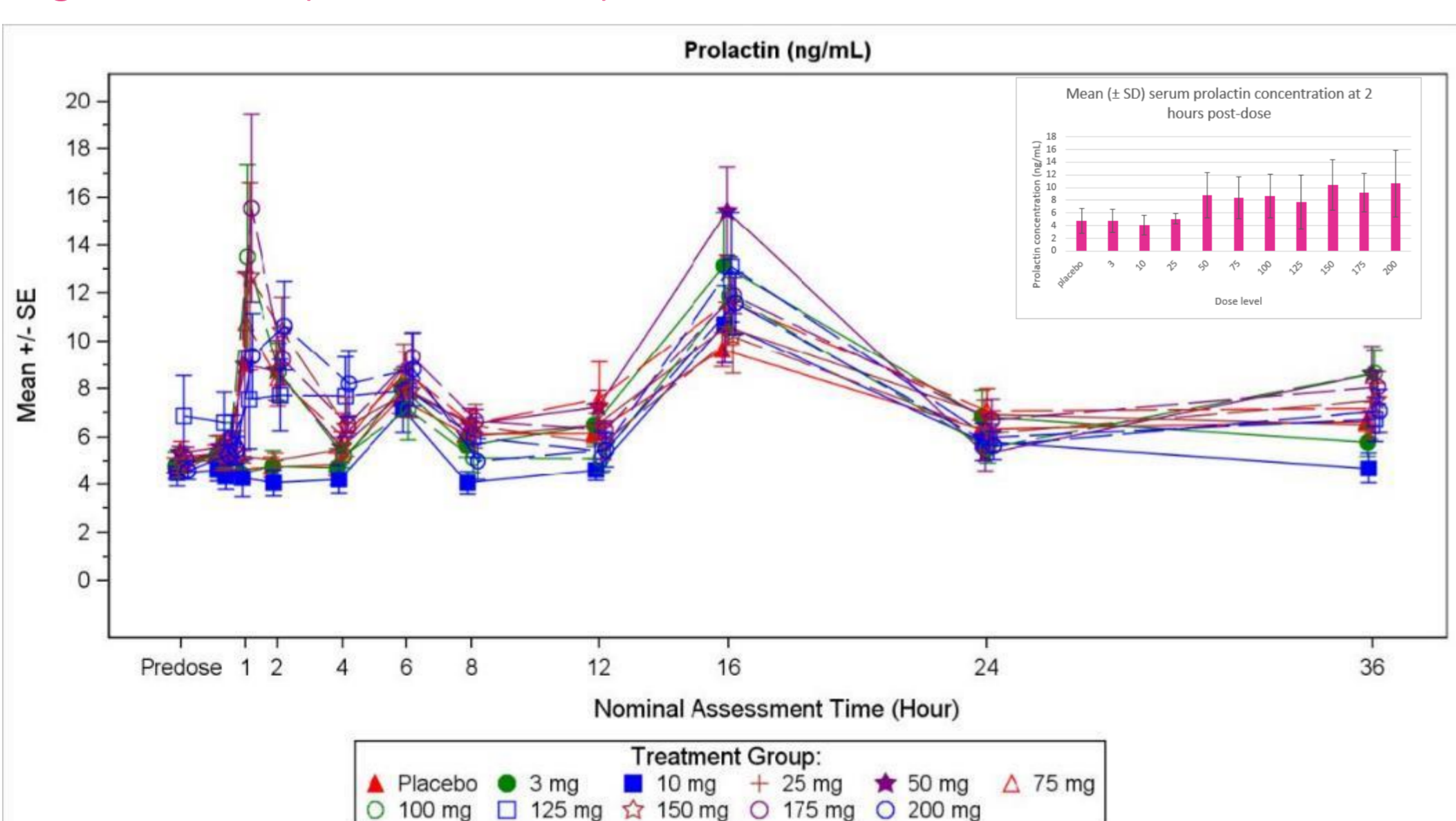


Figure 3. Least Squares Mean Change from Baseline over time Left Pupil/Iris Ratio

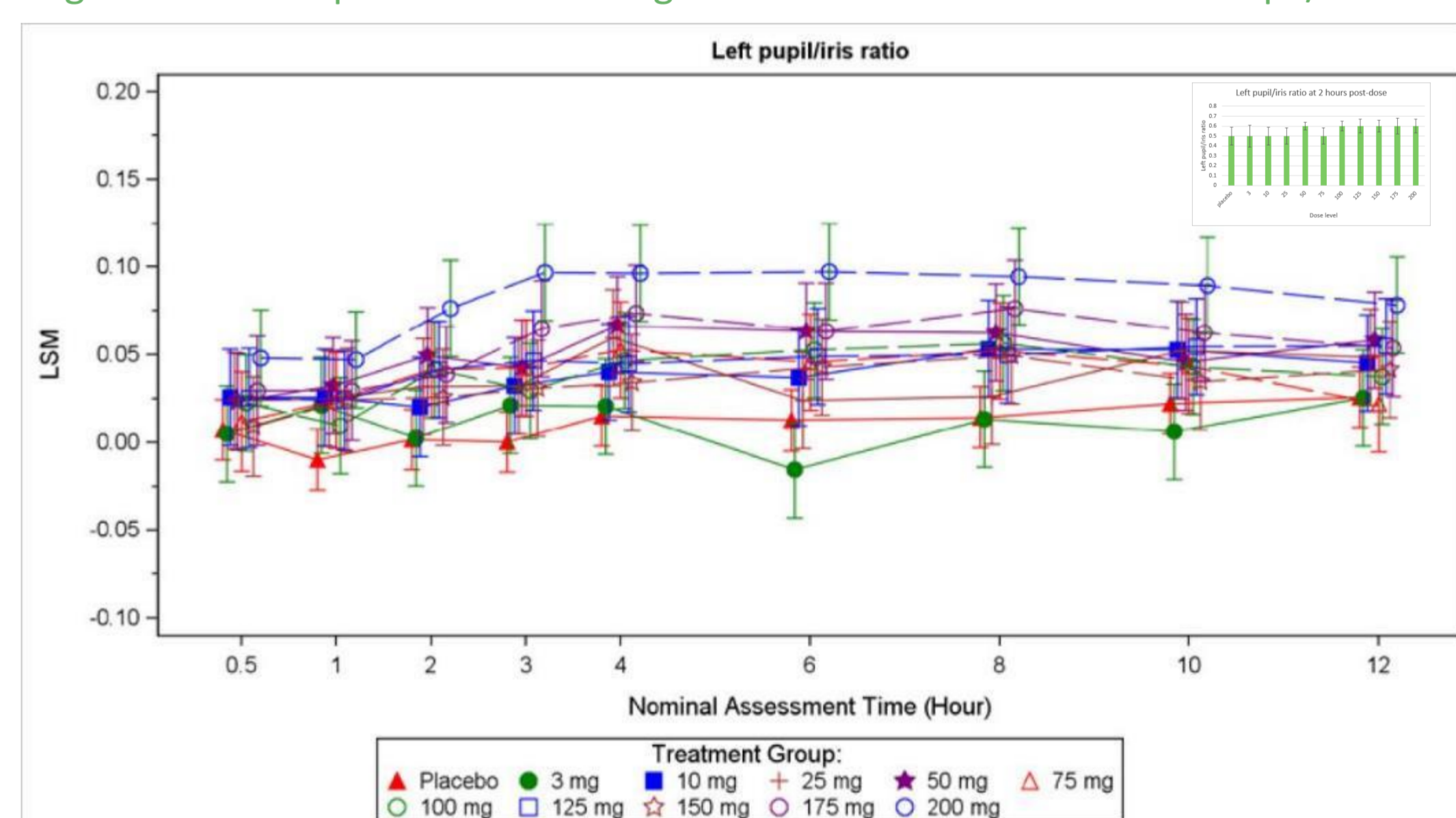


Figure 4. Least Squares Mean Change from Baseline over time Right Pupil/Iris Ratio

