

ML-007C-MA, a Novel Investigational M<sub>1</sub>/M<sub>4</sub> Muscarinic Agonist in Phase 2 Development for the Treatment of Alzheimer’s Disease Psychosis

P2-01

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Introduction

Muscarinic agonists have emerged as a new class of therapeutic agents for the treatment of psychosis with a mechanism distinct from typical and atypical antipsychotics. M<sub>1</sub> and M<sub>4</sub> receptor subtypes show the highest expression in brain regions implicated in psychosis, cognition, and negative symptoms, and thus have therapeutic potential across several neuropsychiatric disorders including Alzheimer’s disease psychosis and schizophrenia. ML-007C-MA is an investigational fixed-dose combination of a novel M<sub>1</sub>/M<sub>4</sub> muscarinic agonist, ML-007 and fesoterodine fumarate, a peripherally-acting muscarinic antagonist. Fesoterodine is ideally suited for the combination due to its low brain penetration, predictable pharmacokinetics, and favorable physicochemical properties that enabled precision matching of the exposure profiles. By synchronizing the pharmacokinetic exposures of agonist and antagonist components in the periphery, ML-007C-MA was designed to maintain strong activation of M<sub>1</sub> and M<sub>4</sub> receptors in the brain to drive efficacy while mitigating cholinergic side effects that can result from modulation of muscarinic receptors in the periphery.

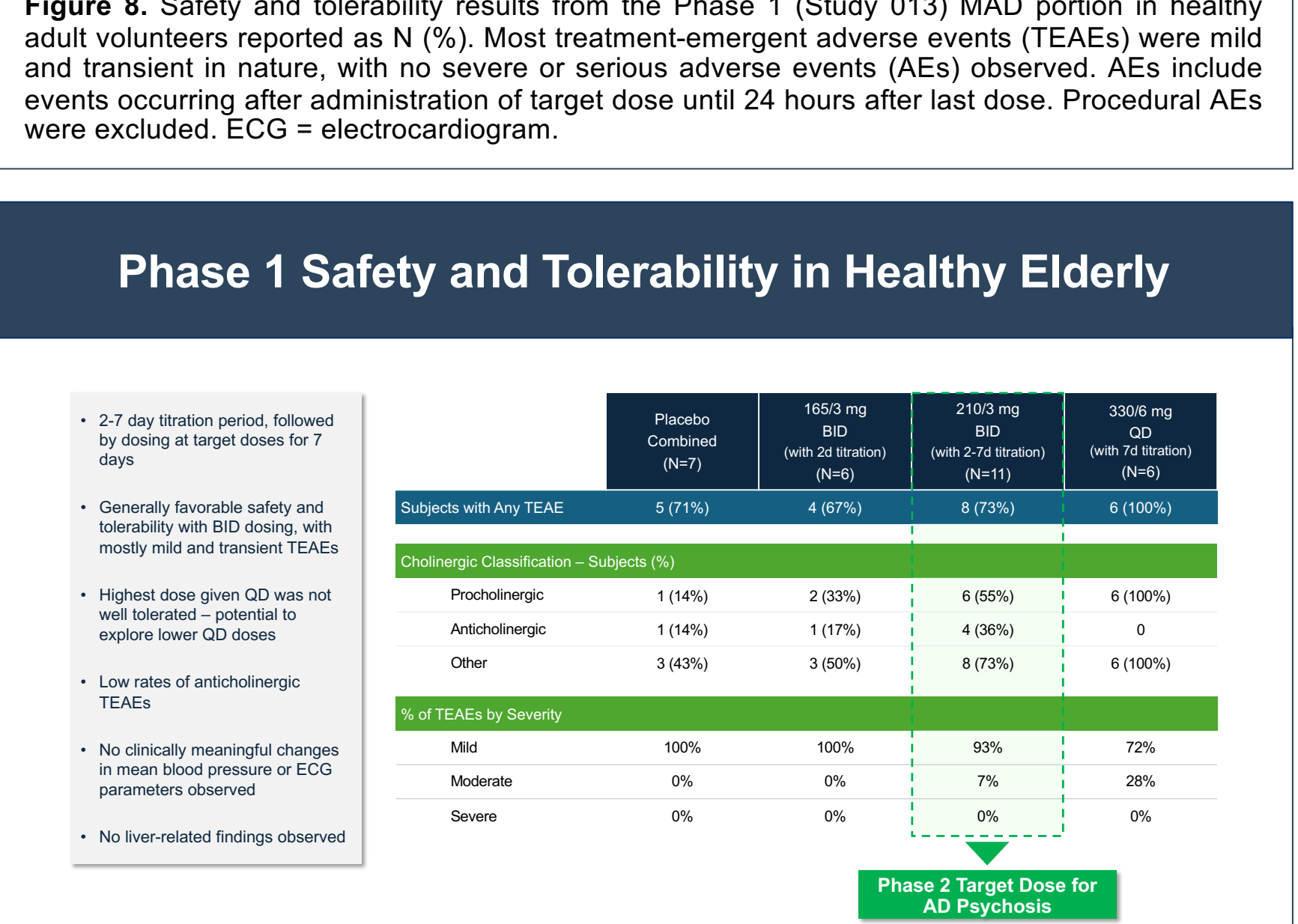
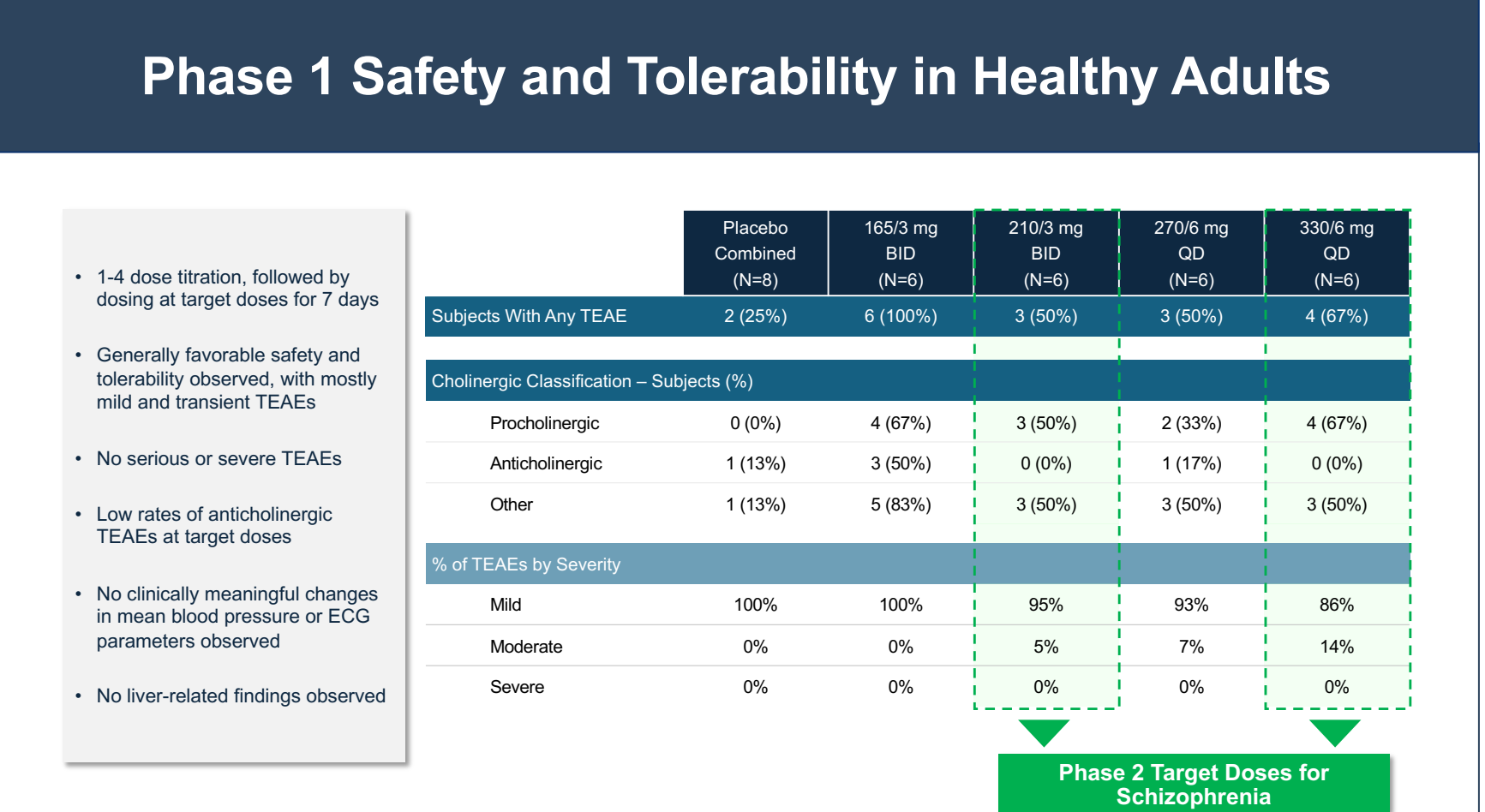
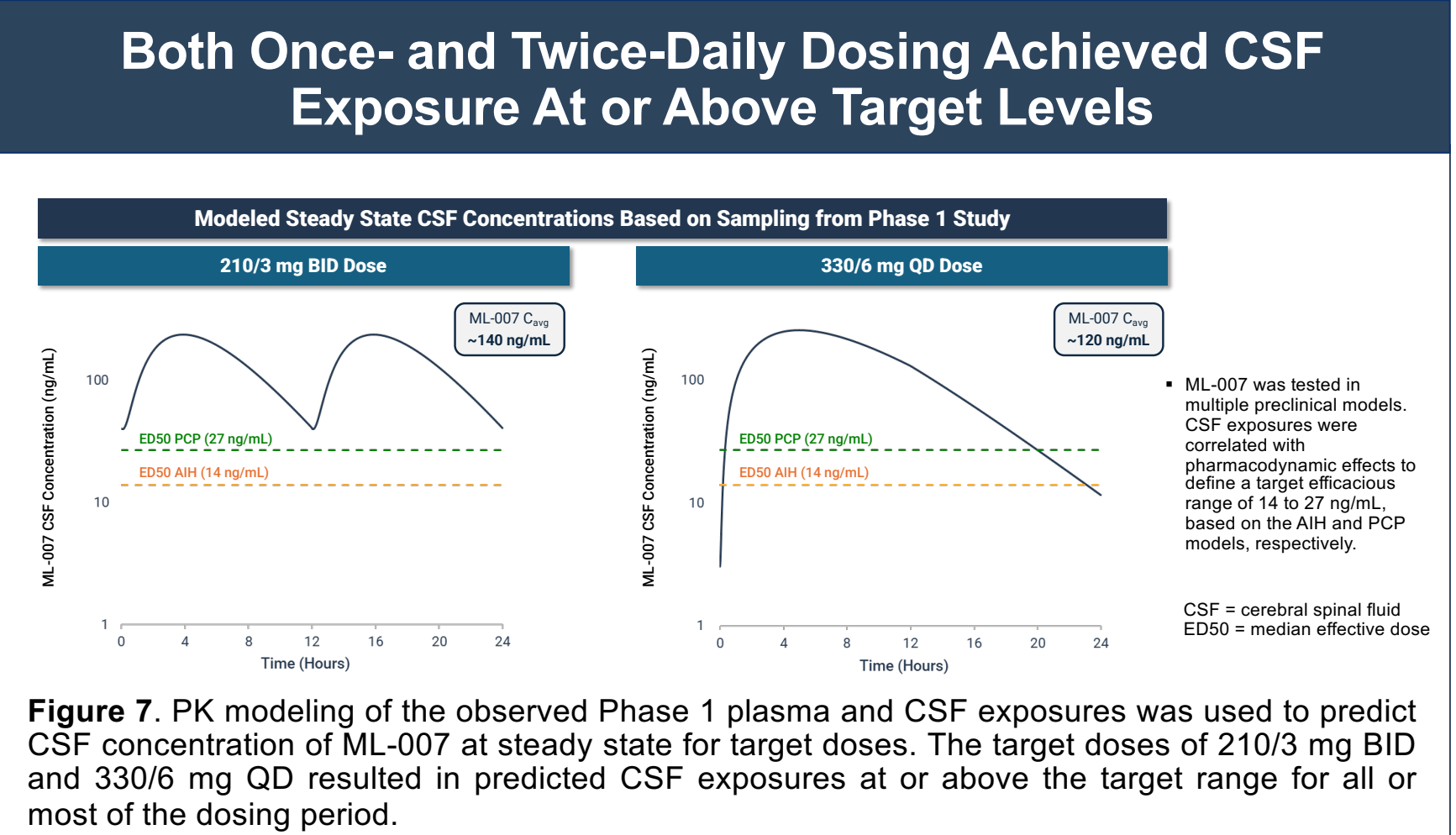
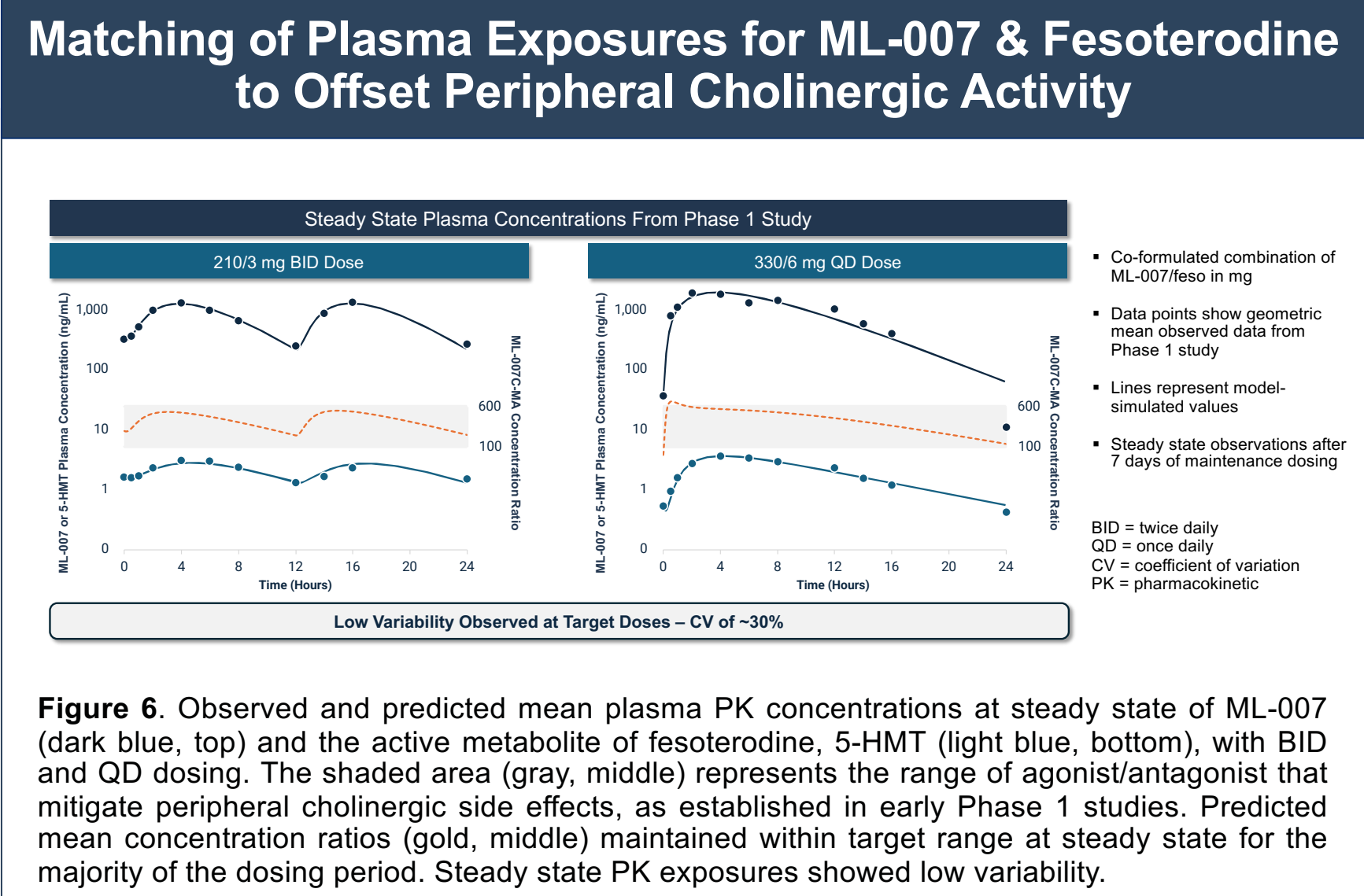
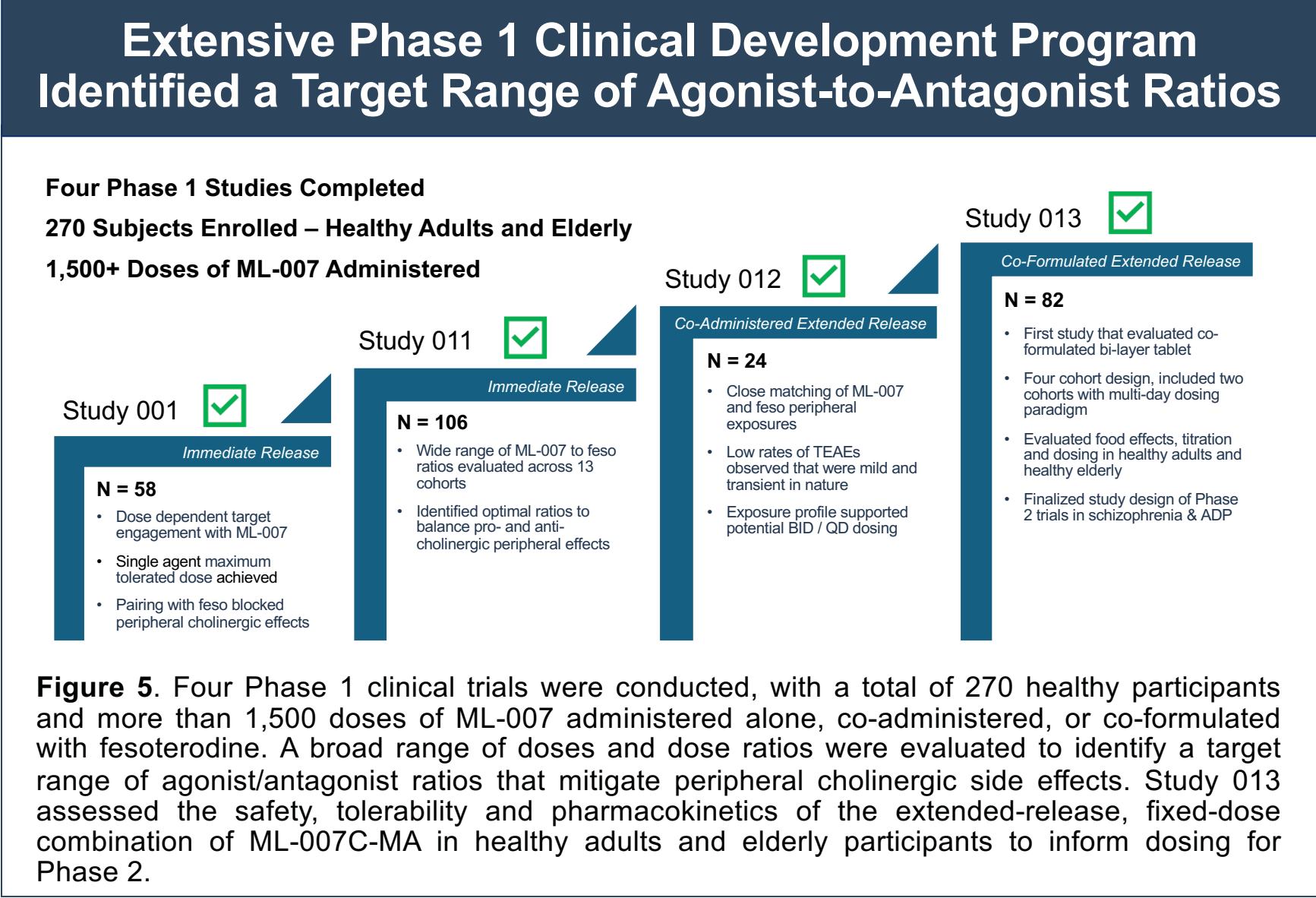
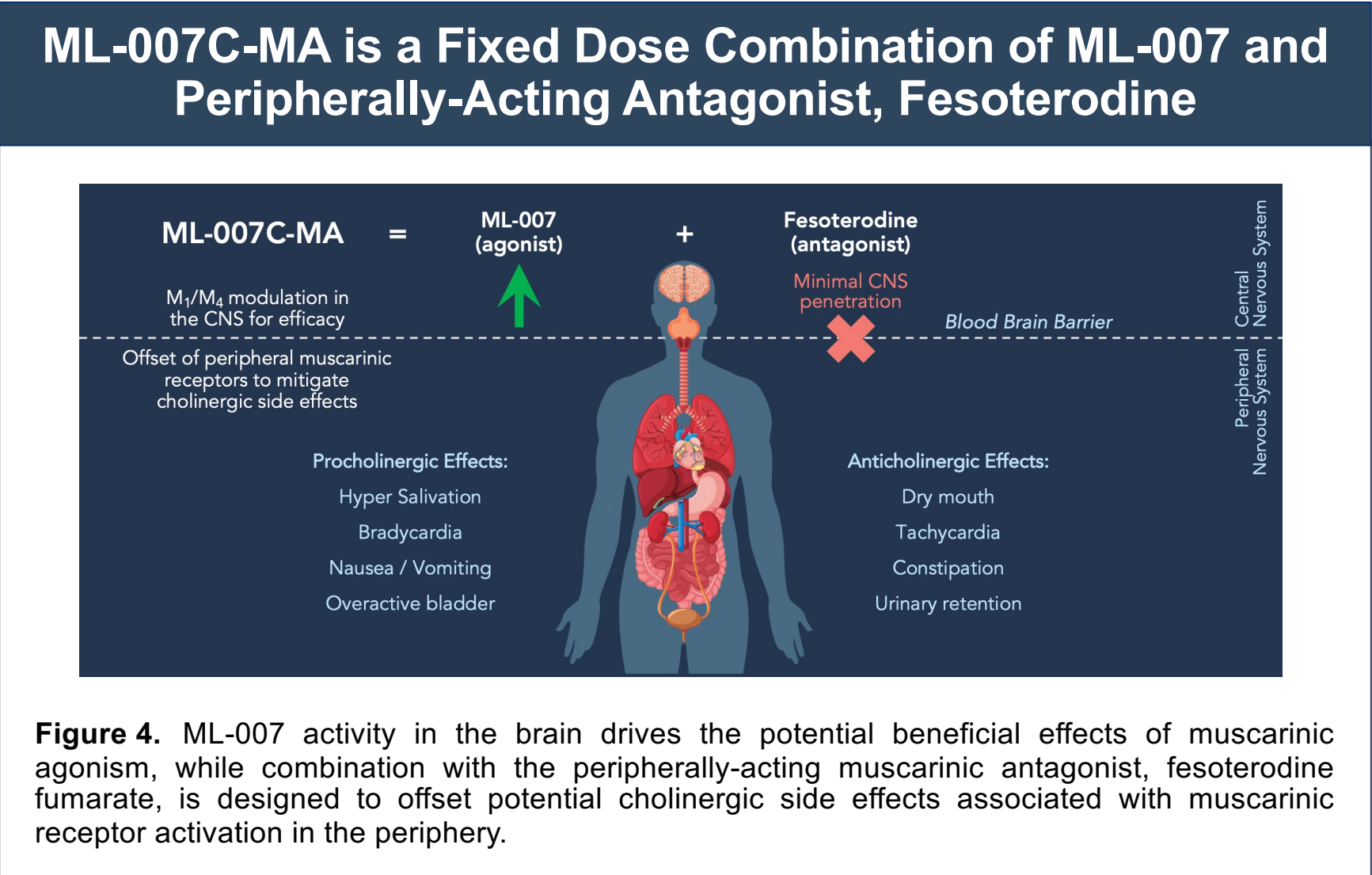
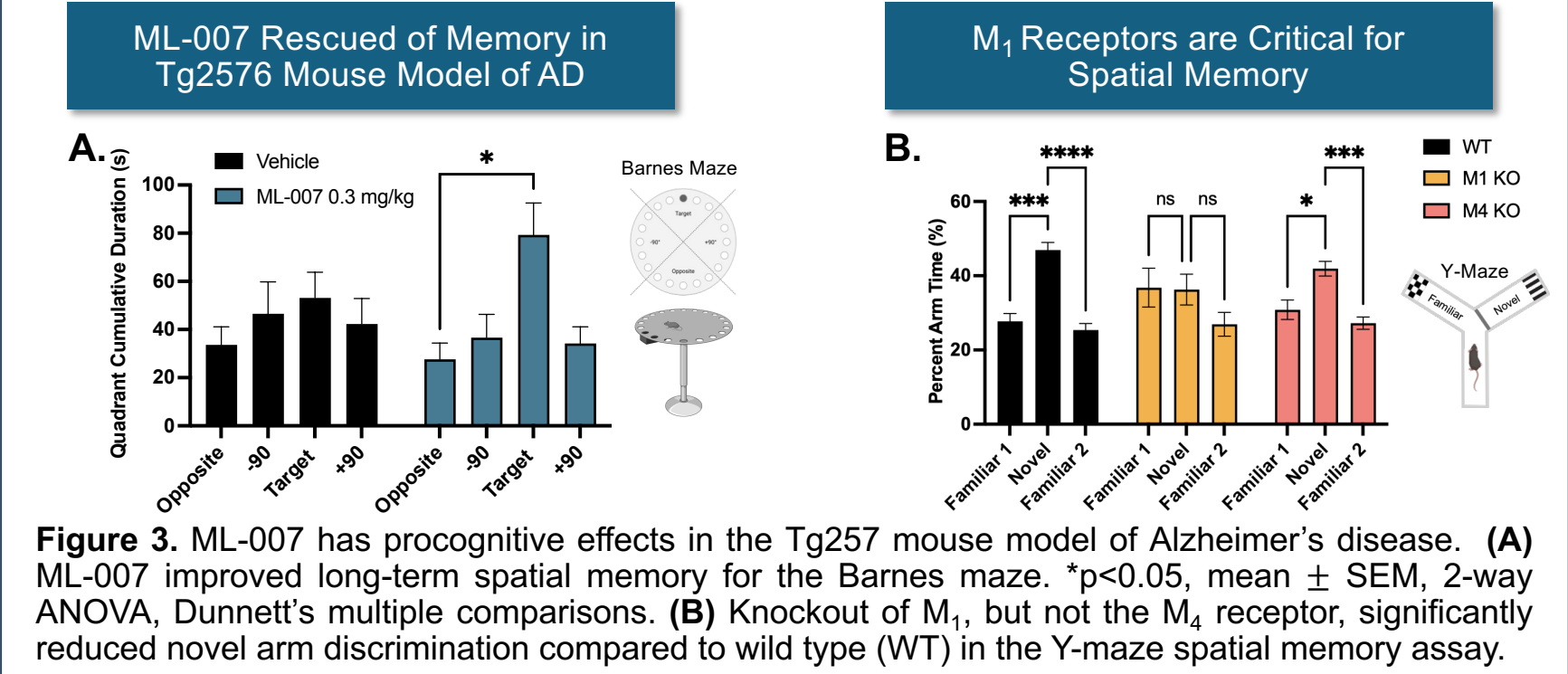
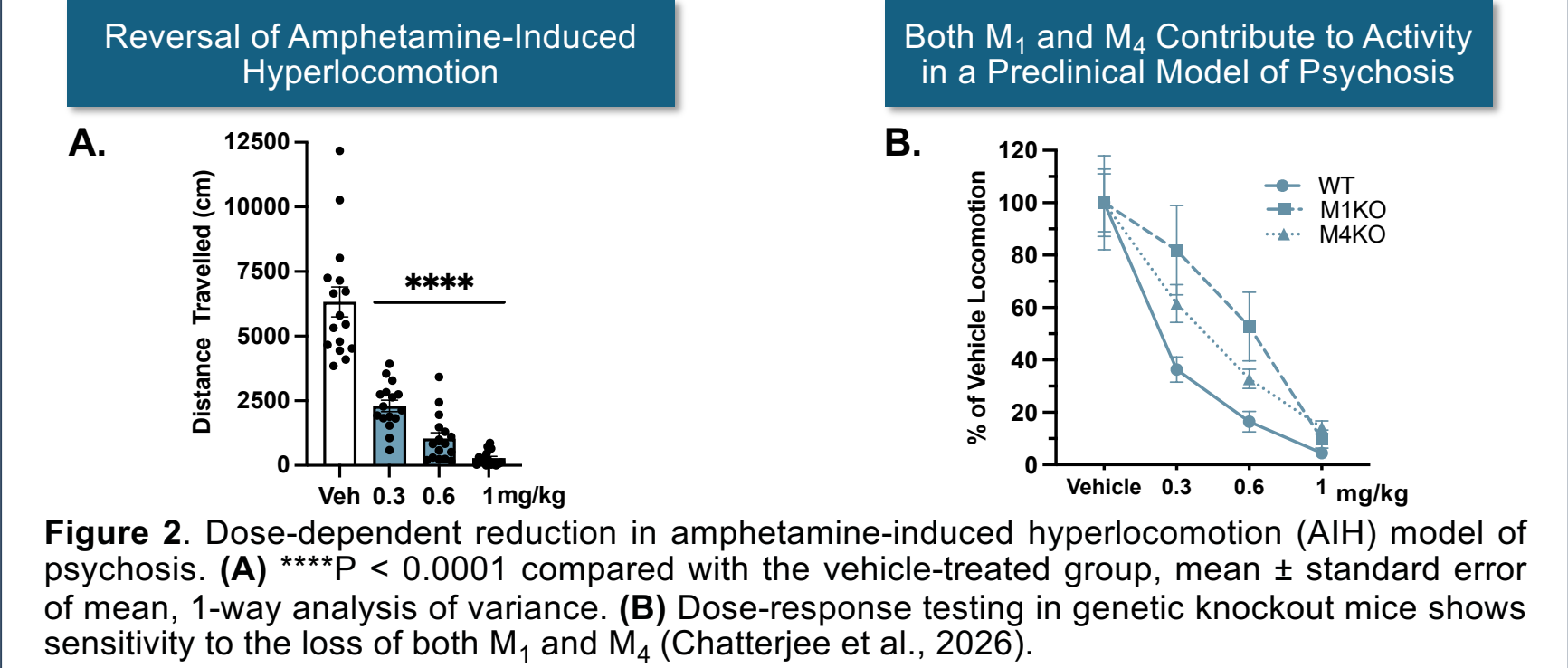
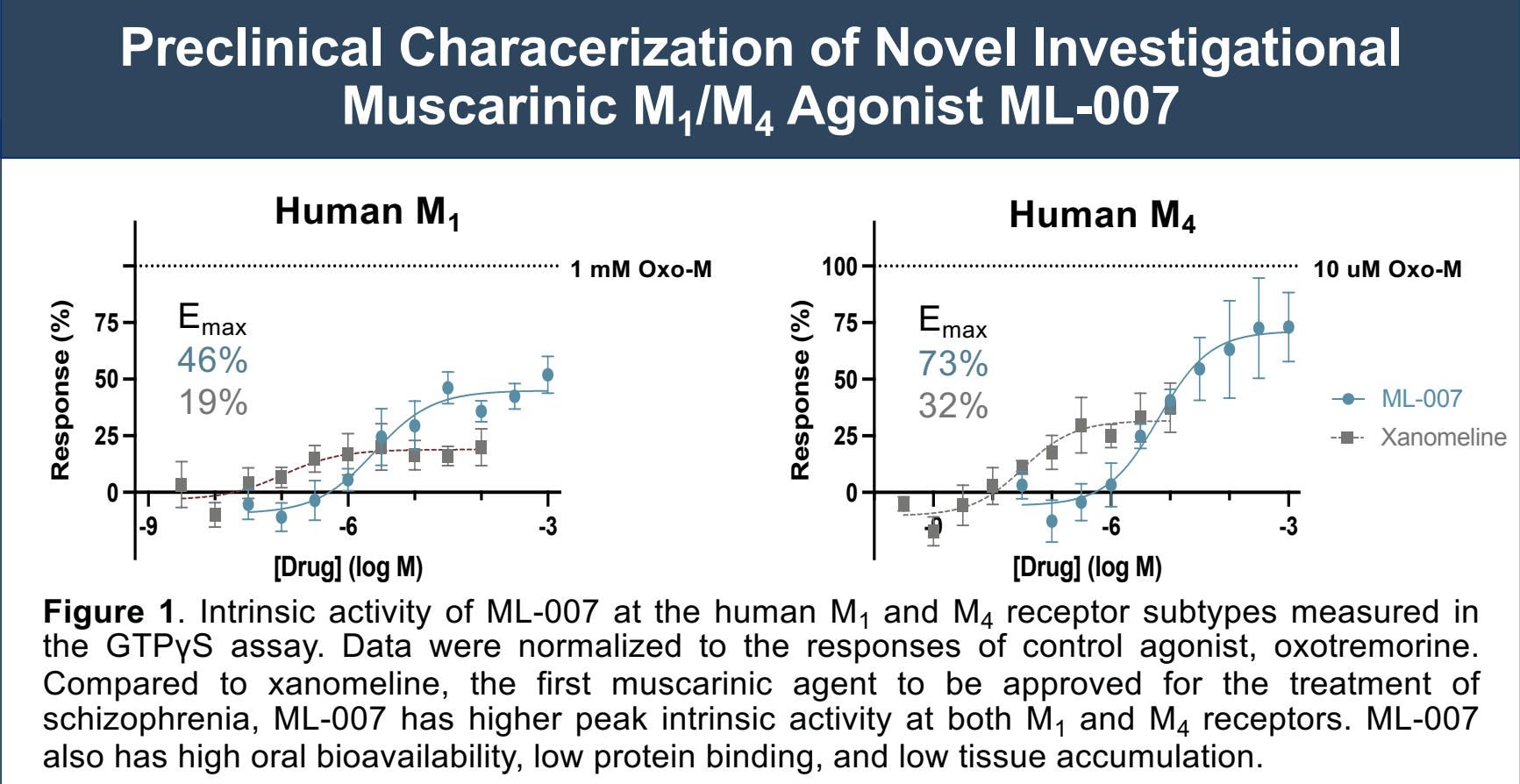
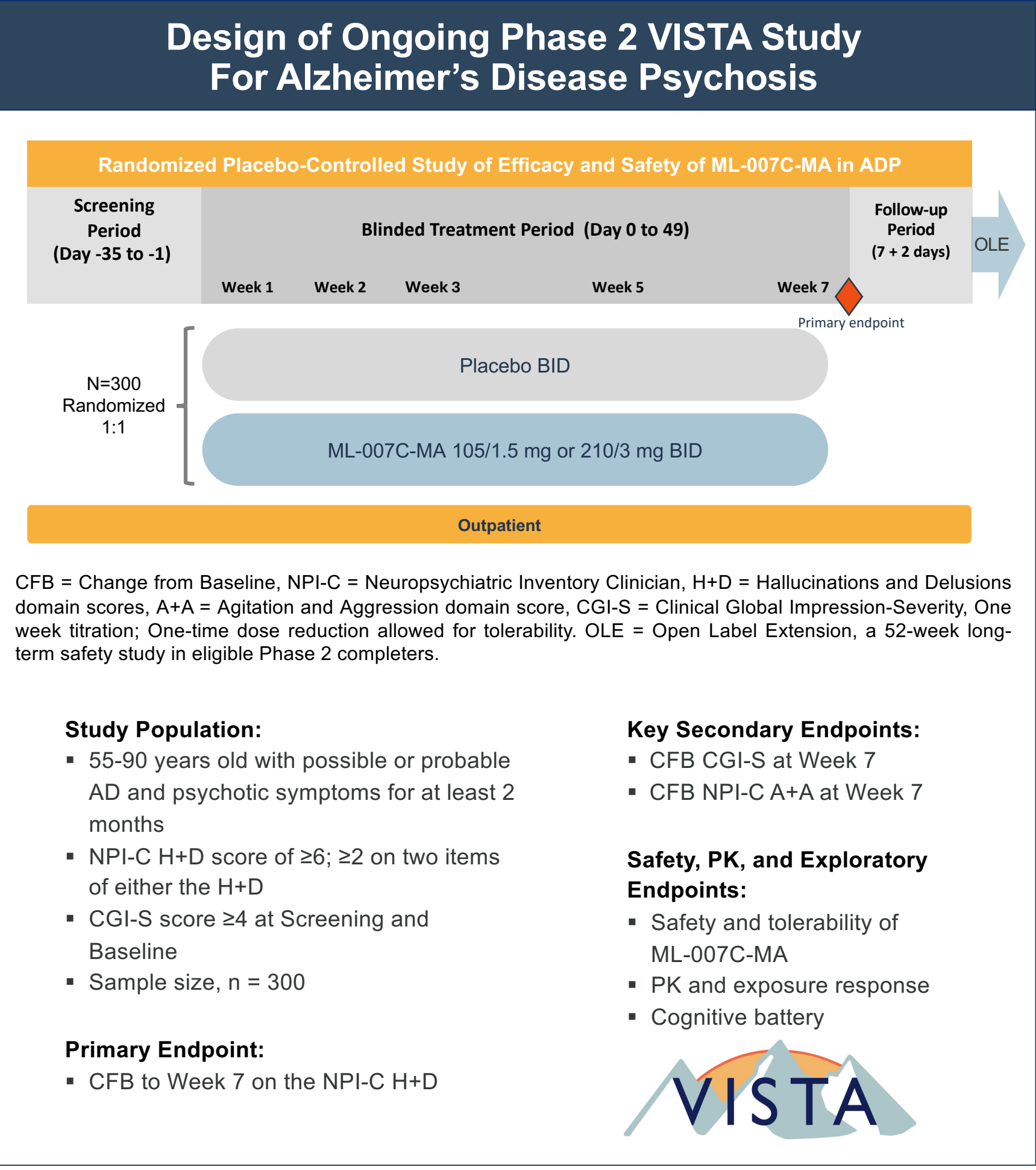


**Figure 9.** Safety and tolerability results from the Phase 1 (Study 013) MAD portion in healthy elderly volunteers reported as N (%). Most treatment-emergent adverse events (TEAEs) were mild and transient in nature, with no severe or serious adverse events (AEs) observed. AEs include events occurring after administration of target dose until 24 hours after last dose. Procedural AEs were excluded. ECG = electrocardiogram.



Conclusions

- ML-007C-MA is an investigational fixed dose combination of ML-007, a novel M<sub>1</sub>/M<sub>4</sub> agonist, and the approved peripherally-acting muscarinic antagonist, fesoterodine
- An extensive Phase 1 clinical development program identified a target range of agonist-to-antagonist ratios to mitigate peripheral cholinergic AEs
- Both once- and twice-daily dosing achieved plasma and CSF exposures that were maintained at or above anticipated clinically relevant levels at target doses selected for Phase 2
- ML-007C-MA was generally well tolerated with no fasting and minimal titration required at doses selected for Phase 2
- ML-007C-MA is currently being evaluated in two Phase 2 clinical trials: the VISTA trial for Alzheimer’s disease psychosis and the ZEPHYR trial for schizophrenia

References

Chatterjee S, Soria M, Norville ZC, Thompson KR, Lillie J, Kreitzer AC, Wood MW. Preclinical efficacy of the muscarinic agonist ML-007 in psychosis models depends on both M<sub>1</sub> and M<sub>4</sub> receptors. Neuropsychopharmacology. 2026 Apr;51(5):840-845.

DISCLOSURES: All authors are employees of MapLight Therapeutics, Inc.

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