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Featured Article

Randomized, controlled, proof-of-concept trial of MK-7622 in Alzheimer's disease

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Abstract

Introduction: We evaluated the selective M1 muscarinic positive allosteric modulator, MK-7622, as adjunctive cognitive enhancing therapy in individuals with Alzheimer's disease.

Methods: A randomized, double-blind, proof-of-concept trial was performed. Participants with mild-to-moderate Alzheimer's disease, being treated with an acetylcholinesterase inhibitor, were randomized 1:1 to 45 mg of MK-7622 or placebo for 24 weeks. Endpoints included the mean change from baseline in Alzheimer's Disease Assessment Scale–Cognitive Subscale ($ADAS\text{-}Cog_{11}$) at 12 weeks and Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory at 24 weeks.

Results: Two hundred forty participants were randomized. The trial was stopped for futility after meeting prospectively defined stopping criteria. MK-7622 did not improve cognition at 12 weeks (group difference in $ADAS\text{-}Cog_{11}$: 0.18 [95% CI: −1.0 to 1.3]) or function at 24 weeks (group difference in Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory: 0.06 [95% CI: −2.4 to 2.5]). More participants taking MK-7622 discontinued study medication because of adverse events than those taking placebo (16% vs 6%) and who experienced cholinergically related adverse events (21% vs 8%).

Discussion: MK-7622 (45 mg) does not improve cognition or function when used as adjunctive therapy in mild-to-moderate Alzheimer's disease.

Keywords: MK-7622; Alzheimer's disease; Cholinergic; Muscarinic; Allosteric modulator; Clinical trial

Conflict of interest: T.V., J.L., C.A., S.F., H.L., L.S.-A., K.B.M., M.E., and D.M. are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA, and own stock/stock options in the company.

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1. Background

Novel symptomatic therapies are needed for the treatment of Alzheimer's disease (AD). Acetylcholinesterase inhibitors and memantine are the current standard of care but exhibit only modest efficacy and dose-limiting side effects. Alternative approaches to improving cholinergic function in patients with AD have focused on either agonism or modulation of the muscarinic or nicotinic cholinergic receptors [1,2]. Of the five subtypes of muscarinic receptor, the M1 muscarinic receptor is abundantly expressed in the hippocampus, cortex, and other brain regions associated with cognitive function, whereas the other muscarinic receptors are more highly expressed in peripheral tissues [1]. The M1 muscarinic receptor likely mediates the procognitive effects of cholinergic agents, whereas other acetylcholine receptors, particularly M2 and M3, may account for side effects [1,3].

Multiple muscarinic agonists have been developed, and several have produced cognitive or behavioral benefits in AD [4–6]. However, these compounds were not selective for M1 and produced intolerable peripheral cholinergic effects such as nausea and salivation. An alternative approach to direct agonism of muscarinic receptors is allosteric modulation [7,8]. MK-7622 is a novel selective M1-positive allosteric modulator that sensitizes the receptor to acetylcholine in the nanomolar range while having no effect on M2, M3, or M4 receptors up to 100 μM [9]. In preclinical studies, MK-7622 restores cognitive function to scopolamine-challenged or cholinergic-depleted animals, induces gamma wave electroencephalogram activity in the hippocampus and cortex, promotes cerebral blood flow, and increases active wakefulness at the expense of delta sleep (i.e., it is an alerting agent) [9]. Importantly, the doses required to produce these effects did not cause overt peripheral cholinergic stimulation.

In humans, MK-7622 has a T_{max} of 3–5 hours and a half-life of ∼26–38 hours, which permits daily dosing. In a phase-1 healthy-volunteer study, MK-7622 at doses of 10, 40, and 70 mg showed a dose-related tendency to increase sigma (12–15 Hz) band awake electroencephalogram activity versus placebo, indicative of an alerting effect, with statistically significant increases at the 40 and 70 mg doses at 2, 4, and 8 hours after dose administration [9]. Furthermore, in another phase-1 study, MK-7622 at doses of 1, 10, and 70 mg reversed scopolamine impairment as measured by a detection task (an assessment of psychomotor function and information processing) from 1 to 4 hours [9]. These observations suggest blood-brain penetration of MK-7622 with pharmacodynamic effects at the administered doses.

The primary efficacy objective of the current trial was to establish proof of concept for MK-7622 as adjunctive therapy to acetylcholinesterase inhibitors in improving cognition in individuals with mild-to-moderate AD after 12 weeks of treatment. The trial also assessed safety and tolerability for up to 24 weeks of treatment. A 45-mg dose of MK-7622 was selected for evaluation based on indirect evidence of target modulation (described previously) and tolerability at this dose in phase-1 studies. Mechanistically, it is hypothesized that acetylcholinesterase inhibitors and MK-7622 have synergistic effects. As a positive allosteric modulator, MK-7622 selectively potentiates the action of acetylcholine at the M1 receptor, but in the absence of acetylcholine, it has only the modest activity at the M1 receptor. Acetylcholinesterase inhibitors increase synaptic levels of acetylcholine by inhibiting the breakdown of acetylcholine with the enzyme acetylcholinesterase, thereby making more acetylcholine available at the receptor site.

2. Methods

Full details of the study methods and statistical analysis are provided in the study protocol that is available as supplementary material (Supplementary material 1).

2.1. Participants

Eligible participants were aged 55–85 years and met criteria for a diagnosis of probable AD based on the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria [10] as well as the criteria for AD dementia in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision [11]. Individuals had an MRI scan consistent with the diagnosis of AD within the last 12 months and a score of 12–24 on the Mini Mental State Examination (MMSE) at screening [12]. Participants were on a stable dose of either donepezil (10 mg daily), rivastigmine (9.5 or 13.3 mg/24 hours for the patch or 6–12 mg total daily dose for the capsule), or galantamine (16–24 mg total daily dose) for at least 2 months before the trial. They also had a reliable and competent trial partner who could accompany them to clinic visits. Major exclusion criteria included evidence of vascular dementia as suggested by a modified Hachinski Ischemia score of >4 [13], clinically significant stroke, or MRI signs of significant cerebrovascular disease; clinically relevant neurological disorder other than AD; clinically relevant or unstable psychiatric disorder, including schizophrenia or other psychotic disorder, bipolar disorder, major depression (unless in remission), substance abuse disorders, or delirium; or significant laboratory screening test abnormality.

2.2. Study design and treatment

This randomized, placebo-controlled, parallel-group, multicenter, double-blind trial (Merck Protocol MK-7622−012; ClinicalTrials.gov NCT01852110) was