

Study Design of MINDSET-1 and MINDSET-2: Efficacy and Safety of Xanomeline and Trospium for Cognitive Impairment in Alzheimer’s Disease

Trials in Progress

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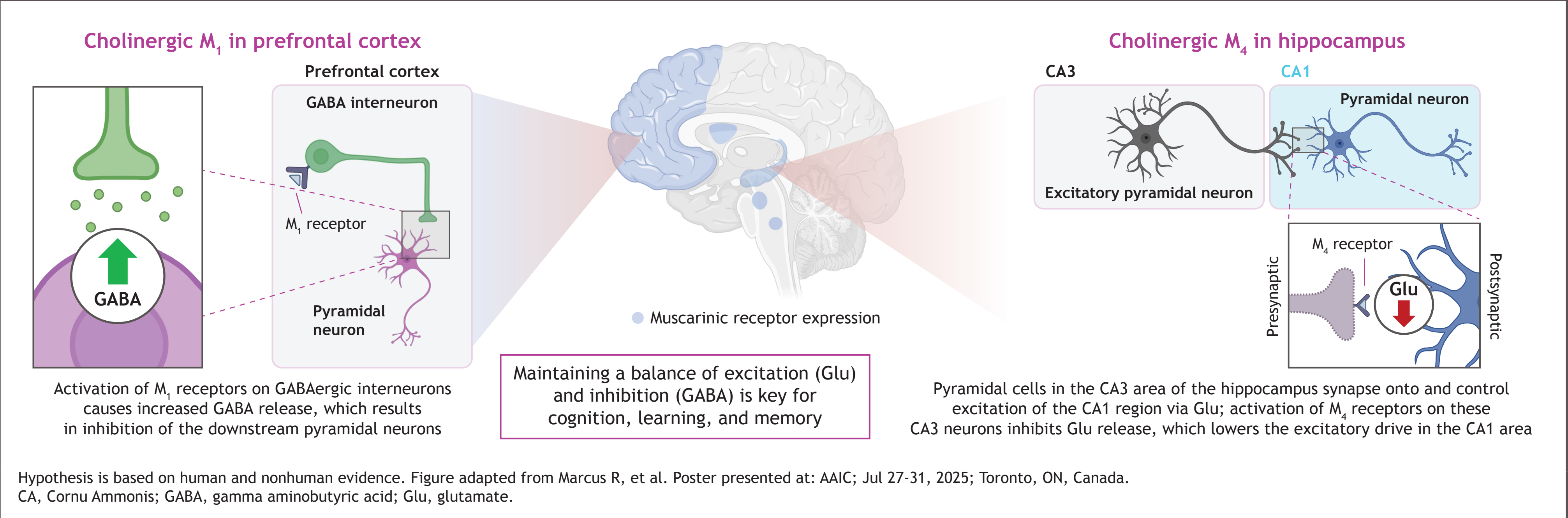
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Background

- Alzheimer’s disease (AD) is the most common cause of dementia¹ and is characterized by a progressive cognitive decline in semantic and executive abilities and memory impairment²⁻⁴
- Treatments that further improve cognitive function and address neuropsychiatric symptoms⁵ are needed
- Previous research on xanomeline, an M₁/M₄-preferring muscarinic receptor agonist, demonstrated improvements in cognitive and behavioral symptoms in individuals with AD; however, cholinergic adverse events (AEs) associated with peripheral muscarinic receptor activation halted further assessment⁶⁻⁸
- Xanomeline/trospium chloride (KarXT) combines xanomeline with the peripherally restricted muscarinic receptor antagonist trospium chloride to reduce peripheral AEs related to xanomeline and is the first muscarinic receptor agonist approved by the US Food and Drug Administration for the treatment of schizophrenia⁹
- Post hoc analyses of the pivotal short-term EMERGENT trials showed that KarXT improved cognitive symptoms in participants with baseline cognitive impairment¹⁰
- Previous clinical data and the mechanism of action suggest that KarXT may be effective in treating AD symptoms

M₁ and M₄ receptor activation may restore excitation/inhibition balance in brain regions associated with cognitive symptoms¹¹



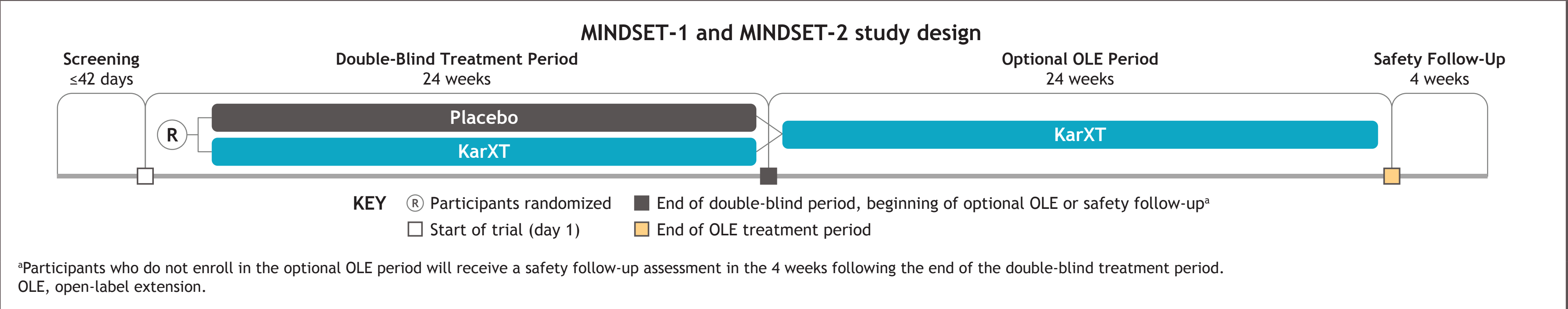
Objectives

- The objectives of the MINDSET trials are to evaluate the efficacy and safety of KarXT in the treatment of cognitive impairment associated with mild to moderate AD

Methods

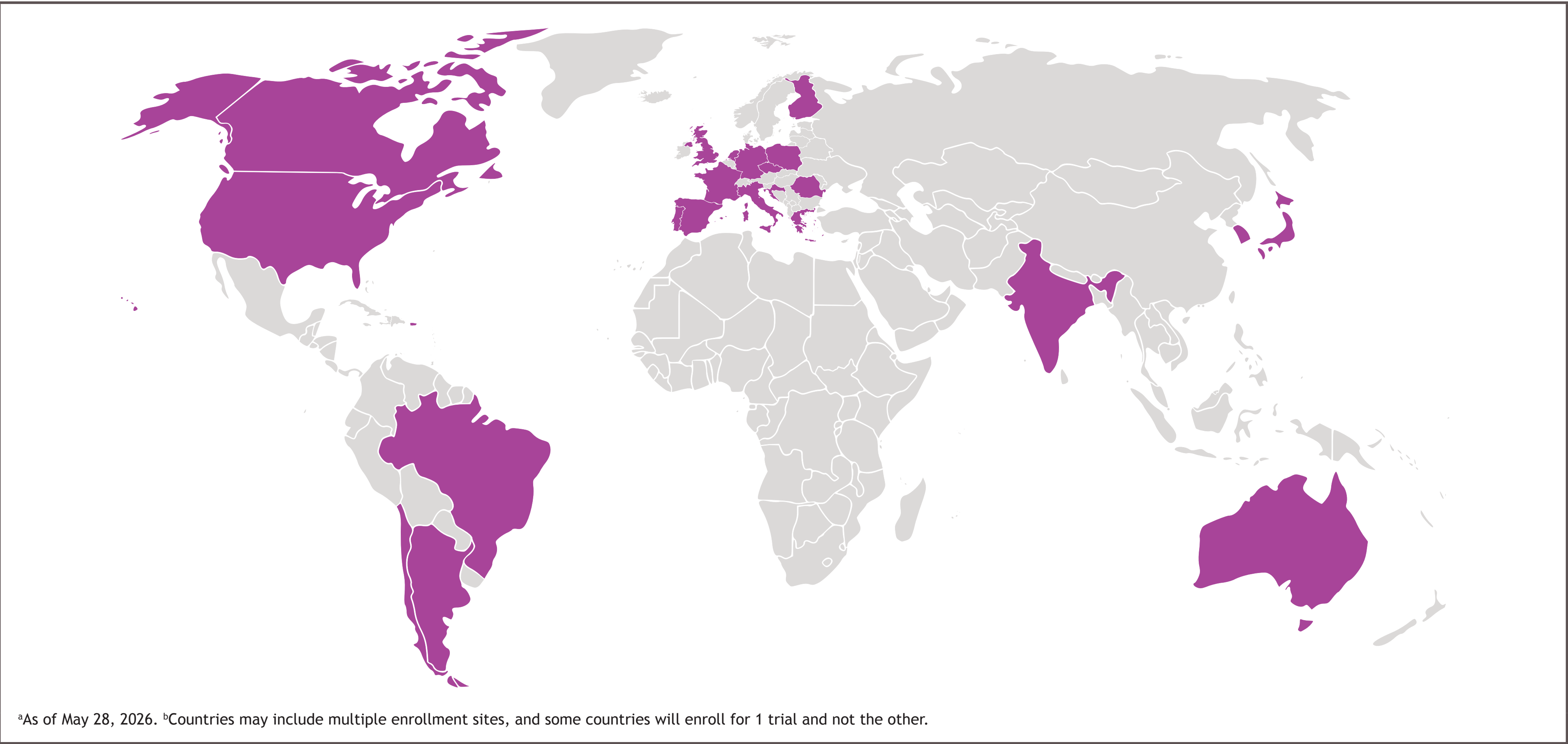
Trial designs

- MINDSET-1 (NCT06976216) and MINDSET-2 (NCT06976203) are identical, global, phase 3, randomized, double-blind, placebo-controlled, parallel group trials designed to evaluate the efficacy and safety of KarXT in the treatment of cognitive impairment associated with mild to moderate AD



Enrollment sites

- The currently recruiting trials will randomize approximately 586 participants each across 106 sites (MINDSET-1) and 126 sites (MINDSET-2)^{a,b}



Key inclusion and exclusion criteria

Key inclusion criteria ^a	
	Males and females aged 60 to 85 years
	Confirmed diagnosis of mild (stage 4) or moderate (stage 5) AD-related dementia consistent with 2024 revised criteria for diagnosis and staging of AD: Alzheimer's Association Workgroup using a stepwise diagnostic approach - Historical evidence of AD pathology with: - Amyloid PET - CSF AB42/40 ratio OR CSF pTau181/AB42 ratio OR plasma pTau217/AB42 ratio OR - If no historical evidence or does not satisfy other requirements, use: - Plasma biomarker^b OR amyloid PET OR CSF AB42/40 ratio or pTau181/AB42 ratio
	MMSE score ranging from 12 to 22, inclusive, at the time of screening
	Has a designated caregiver who maintains adequate contact (≥10 hours/week) who is willing to participate in the trial
	Participants on AChEs and/or memantine must be on a stable dose for ≥12 weeks prior to screening and agree to maintain the stable dose for the trial duration
Key exclusion criteria ^a	
	Any significant or severe medical conditions that could compromise safety of the participant, their ability to comply with or complete the trial, or the integrity of trial results
	Any primary psychiatric diagnoses, including major depression ^c , schizoaffective disorder, or bipolar disorder, or any severe psychiatric symptoms
	Previous exposure to KarXT or treatment with disease-modifying anti-amyloid therapies for AD within 6 months prior to screening
	Significant pathological findings on brain MRI at screening that could affect safety or interfere with trial procedures

^aNot a full list of inclusion or exclusion criteria. ^bPer regulatory-accepted guidelines. ^cDepression was defined as a Geriatric Depression Scale-Short Form score ≥8 at screening. AB, amyloid β; AChE, acetylcholine esterase inhibitor; AD, Alzheimer's disease; CSF, cerebrospinal fluid; KarXT, xanomeline/trospium chloride; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PET, positron emission tomography; pTau, phosphorylated tau.

Trial objectives and outcome measures

Objectives	Endpoints (at Week 24)	Efficacy Scale Descriptions
Primary	Efficacy of KarXT compared with placebo - Change from baseline in ADAS-Cog-11 CIBIC+	- Comprises 11 items that assess memory, orientation, language, and praxis; higher score = greater cognitive impairment - Interview with participants and their caregivers that measures change in global function across 4 domains (general condition, cognitive function, behavior, and ADLs); 7-point scale: 4 = no change, >4 = worsening, <4 = improvement
Secondary	Efficacy of KarXT compared with placebo - Change from baseline in ADCS-ADL - Change from baseline in NPI-10	- Comprises 23 items that assess participant performance of daily tasks over the last 4 weeks^a; higher score = better ADL functioning - Structured 10-item caregiver interview on delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/labability, and aberrant motor activity; higher score = greater psychiatric disturbance
Safety	Safety and tolerability of KarXT compared with placebo - Reported AEs, serious AEs, and AEs of special interest - AEs leading to trial intervention discontinuation, trial discontinuation, or death - Clinically significant changes in vital signs, ECG, C-SSRS, weight, and safety laboratory tests	

^aAdministered by a site rater to the trial partner/caregiver who has regular (ideally daily) contact with the participant. ADAS-Cog-11, 11-item Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL, Alzheimer's Disease Cooperative Study-Activities of Daily Living; ADL, activity of daily living; AE, adverse event; CIBIC+, Clinician's Interview-Based Impression of Change Plus Caregiver Input; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; KarXT, xanomeline/trospium chloride; NPI-10, 10-Item Neuropsychiatric Inventory.

Conclusions

- There is an unmet need for treatment that effectively improves cognition in AD
- MINDSET-1 and MINDSET-2 are identical, global, phase 3, randomized, double-blind, placebo-controlled, parallel group trials evaluating the efficacy and safety of KarXT for the treatment of cognitive impairment associated with mild to moderate AD
- Participant enrollment began July 2025 with primary completion projected for September 2028
- Pending the efficacy and safety results from the MINDSET program, KarXT has the potential to be a first-in-class treatment for cognition in mild to moderate AD, with a unique mechanism of action based on muscarinic receptor agonism

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Acknowledgments

- The authors thank the participants and families engaging in these trials as well as the clinical study teams
- The trials are supported by Bristol Myers Squibb
- All authors contributed to and approved the poster; editorial assistance was provided by Deja Scott-Shemon, MPH, of Peloton Advantage, LLC, an OPEN Health company, funded by Bristol Myers Squibb
- Authors would also like to acknowledge Ashish Shah, PharmD, of Bristol Myers Squibb for contributions to the concept and trial design

Disclosures

- JLC: Consultant for Acadia, Acumen, ALZpath, Annovis, Artery, Axsome, Biogen, Biohaven, Bristol Myers Squibb, CervoMed, Cognition Therapeutics, Eisai, Fosun, GAP Foundation, Hummingbird Diagnostics, IGC, Janssen, Kinaxis, Lilly, Lundbeck, LSP/eqt, Merck, MoCA Cognition, Novo Nordisk, NSC Therapeutics, Otsuka, ReMYND, Roche, Scottish Brain Sciences, Signant Health, Sincere, Sinaptica, T-Neuro, and Vaxxinity; Supported by NIA R35AG71476, NIA R25AG083721-01, Alzheimer's Disease Drug Discovery Foundation, Ted and Maria Quirk Endowment, and Joy Chambers-Grundy Endowment
- WPH: Full-time employee of and equity holder in Engrail Therapeutics; Former employee of Bristol Myers Squibb
- DL, JS, and CL: Employees of Bristol Myers Squibb

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