

Study Design for Two Phase 3 Trials of Xanomeline/Trospium (KarXT) for Agitation Associated With Alzheimer's Disease (ADAGIO-1/ADAGIO-2)

Trials in Progress

George Grossberg,¹ Yanqiu Shao,² Ian Ramsay,^{2,*} Ron Marcus,^{2,*} Frank Scheiber,² Rosalinda Sepulveda²

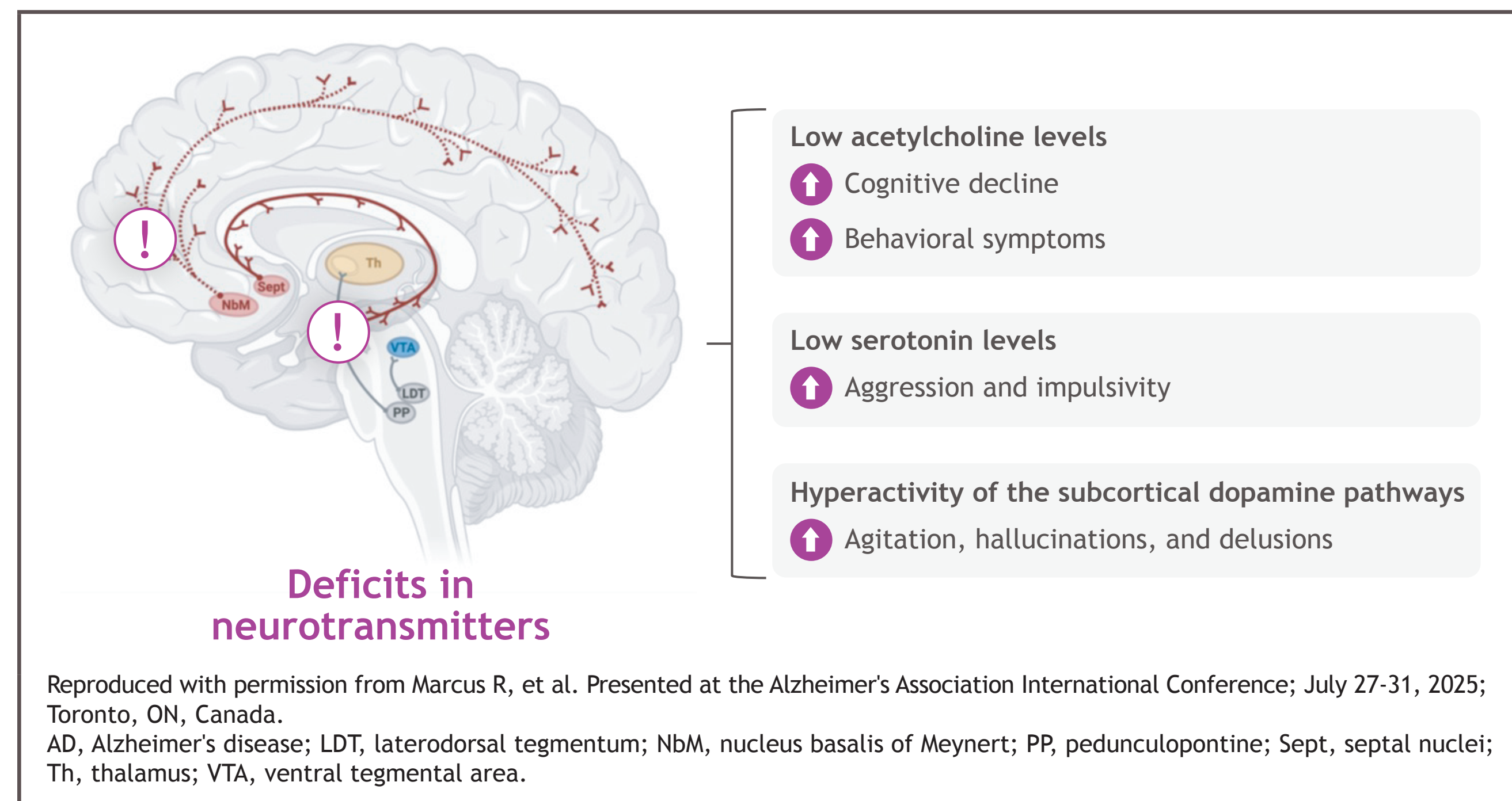
¹Saint Louis University School of Medicine, St. Louis, MO, USA; ²Bristol Myers Squibb, Princeton, NJ, USA

*Employee at the time of study initiation

Background

- Agitation occurs in approximately 45% of individuals with Alzheimer's disease (AD)¹ and is associated with faster disease progression,² decreased quality of life,³ greater caregiver burden,⁴ higher rates of institutionalization, increased mortality, and greater costs of care⁵
- Current treatment options for agitation associated with AD include 1 atypical antipsychotic approved by the US Food and Drug Administration and off-label treatments with considerations of safety, tolerability, and efficacy; new treatment alternatives are warranted
- In AD, brain regions degenerate due to amyloid and tau pathology, including hypoactivity in the prefrontal cortex impairing executive function and impulse control and hyperactivity in the amygdala exaggerating emotional drive, leading to agitation⁶
 - These structural changes are accompanied by deficits in neurotransmitters, including low acetylcholine levels, low serotonin levels, and hyperactivity of the subcortical dopamine pathways (**Figure 1**)⁶

Figure 1. Overview of neurotransmitter deficits associated with neuropsychiatric symptoms of AD⁶⁻⁸



- Xanomeline/trospium chloride (KarXT) is a formulation of xanomeline, a dual M_1/M_4 muscarinic receptor agonist, and trospium chloride, a peripherally restricted pan-muscarinic receptor antagonist, that is approved in the United States for schizophrenia
- In previous research, the M_1/M_4 -preferring muscarinic receptor agonist xanomeline showed antipsychotic activity in AD, but peripheral cholinergic adverse events (AEs) halted further assessment⁹
- Combining xanomeline with trospium chloride has been shown to reduce peripheral cholinergic AEs¹⁰
- In the 5-week, double-blind, placebo-controlled EMERGENT-1, EMERGENT-2, and EMERGENT-3 trials, adults with an acute schizophrenia exacerbation randomized to KarXT experienced significantly greater improvements in agitation compared with those randomized to placebo in each trial individually as well as in pooled post hoc analyses¹¹
- These data suggest that KarXT may be effective in treating symptoms of agitation associated with AD

Objectives

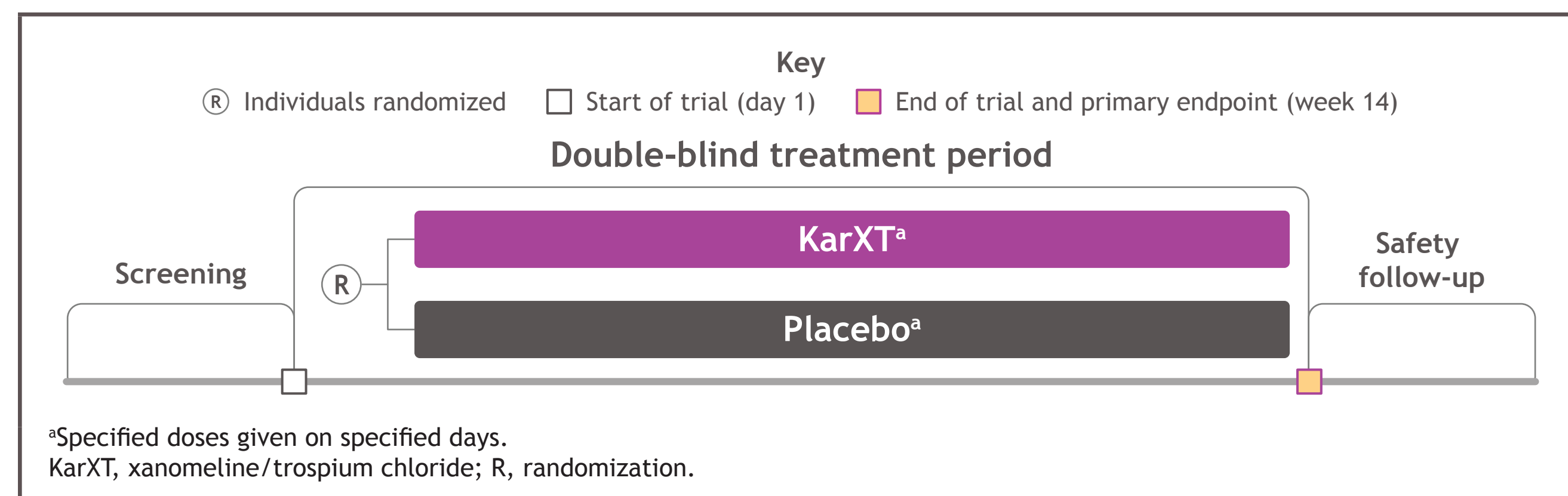
- The objectives of the ADAGIO-1 and ADAGIO-2 trials are to assess the efficacy, safety, and tolerability of KarXT compared with placebo for the treatment of agitation associated with AD

Methods

Study design

- ADAGIO-1 (NCT07011732) and ADAGIO-2 (NCT07011745) are identical, pivotal, randomized, double-blind, placebo-controlled, parallel group, phase 3 trials of adults with agitation associated with AD (**Figure 2**)
- Participants are randomized to receive KarXT or placebo over the 14-week treatment period

Figure 2. Study design schema



- Key inclusion and exclusion criteria are listed in **Table 1**

Table 1. Key inclusion and exclusion criteria^a

Key inclusion criteria

- 55-90 years of age
- Diagnosis of AD in accordance with 2024 Alzheimer's Association criteria with ≥ 1 of the following:
 - Historical evidence of AD diagnosis with amyloid PET, A β 42/40 ratio in CSF, pTau181/A β 42 ratio in CSF, or pTau217/A β 42 ratio in plasma using an HA-authorized diagnostic assay
 - If no historical evidence was available, plasma biomarker was assessed for eligibility and/or one of the following was conducted: amyloid PET or A β 42/40 ratio or pTau181/A β 42 ratio in CSF using an HA-authorized diagnostic assay
- MMSE score of ≤ 24 at screening
- Identified caregiver with sufficient contact (approximately 8 hours/week)
- NPI/NPI-NH agitation/aggression score ≥ 4 at screening and baseline
- CMAI-IPA total score ≥ 30 at screening and baseline
- History of agitation based on IPA consensus definition with onset ≥ 2 weeks prior to screening

Key exclusion criteria

Medical conditions:

- Agitation symptoms primarily attributable to a condition other than AD causing dementia
- History of bipolar disorder, schizophrenia, or schizoaffective disorder or a history of (or at high risk for) urinary retention, gastric retention, or narrow-angle glaucoma
- Risk of suicidal behavior per investigator assessment or C-SSRS

Prior/concomitant therapy:

- Recent history of receiving MAOIs, anticonvulsants, mood stabilizers, tricyclic antidepressants, or any other psychoactive medications except for as-needed anxiolytics was exclusionary
 - SSRIs and SNRIs taken at a stable dose for ≥ 8 weeks prior to screening may be permitted
 - Mirtazapine may be used as a hypnotic and trazodone may be used as a hypnotic or for agitation if started ≥ 8 weeks prior to screening

^aNot a full list of inclusion or exclusion criteria.

AD, Alzheimer's disease; CMAI-IPA, Cohen-Mansfield Agitation Inventory-International Psychogeriatric Association; CSF, cerebrospinal fluid; C-SRRS, Columbia-Suicide Severity Rating Scale; HA, Health Authority; IPA, International Psychogeriatric Association; MAOI, monoamine oxidase inhibitor; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; NPI-NH, Neuropsychiatric Inventory-Nursing Home; PET, positron emission tomography; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Outcomes

- The primary, secondary, and safety endpoints are listed in Table 2

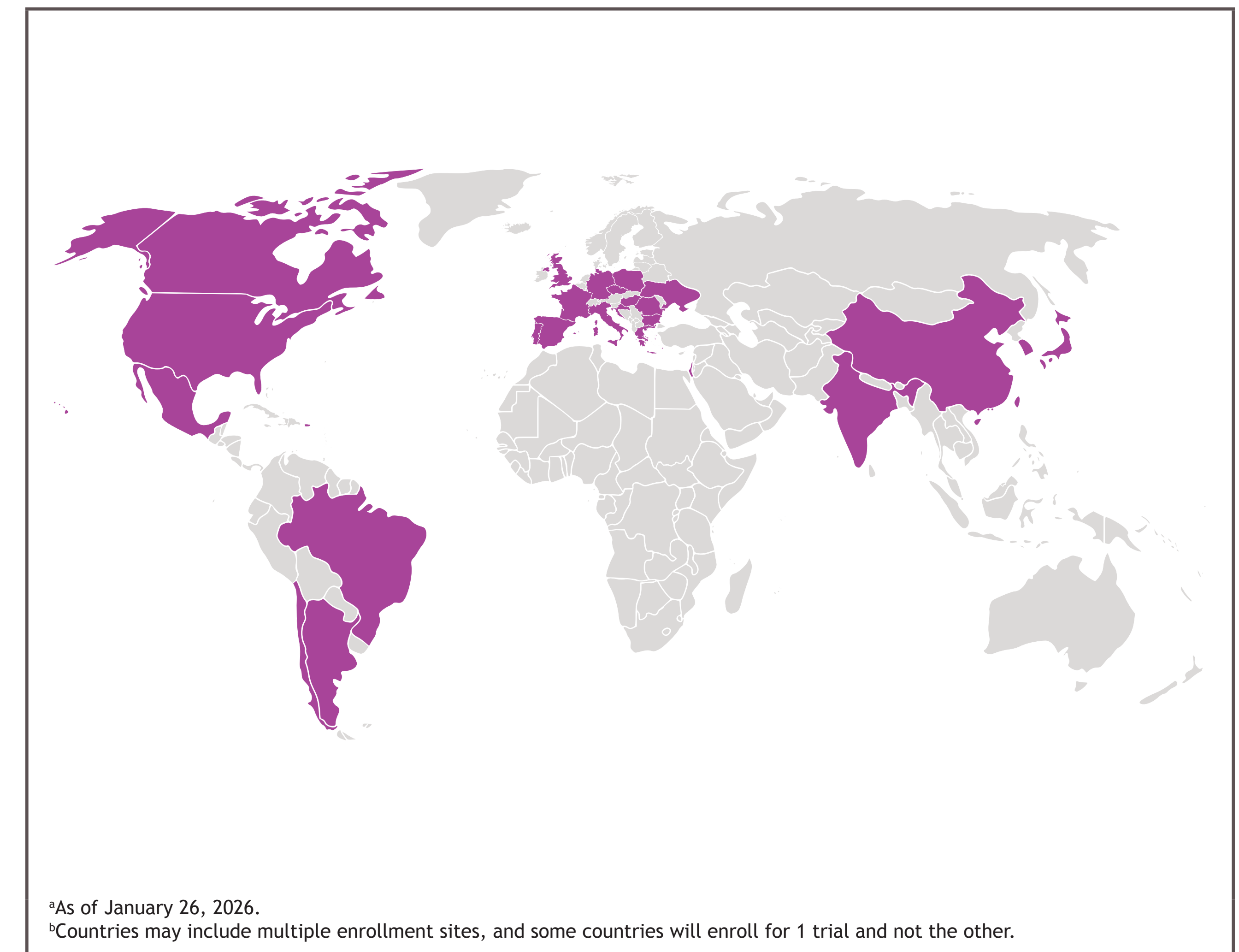
Table 2. Study endpoints

Objectives		Endpoints (at Week 14)	Efficacy Scale Descriptions
Primary	Efficacy of KarXT compared with placebo	Change from baseline in CMAI-IPA total score	CMAI-IPA is a 19-item scale mapping items from CMAI onto IPA agitation criteria domains (physical aggression, excessive motor activity, and verbal aggression)
Key secondary	Efficacy of KarXT compared with placebo	Change from baseline on the CGI-S as it relates to agitation	CGI-S is a 7-point scale rating illness and symptom severity in the past 7 days based on clinician discretion at the time of assessment
Secondary	Efficacy of KarXT compared with placebo	Change from baseline on CMAI-IPA domains	- CMAI is a 29-item rater-led interview of caregivers assessing frequency of agitated behaviors in the previous 2 weeks; scores range from 29 to 203 - NPI is a 5-point, rater-assessed questionnaire administered to caregivers to assess the occurrence, severity, and change in neuropsychiatric symptoms in community-dwelling individuals with brain disorders - NPI-NH is based on the NPI, but rephrased for residents in extended care facilities
		Occurrence of response based on CMAI-IPA ($\geq 30\%$, $\geq 40\%$, and $\geq 50\%$ change from baseline)	
		Change from baseline on CMAI total score and NPI/NPI-NH total score	
	Safety and tolerability of KarXT compared with placebo	- Reported AEs, TEAEs, SAEs, AESIs, and AEs leading to study treatment withdrawal or death - Vital signs, clinical laboratory evaluations, weight, body mass index, 12-lead ECG, suicidal ideation via C-SSRS, BARS, and AIMS scores - Severity of benign prostatic hyperplasia in male participants as assessed by IPSS	

AE, adverse event; AEFI, adverse event of special interest; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CGI-S, Clinical Global Impressions-Severity; CMAI, Cohen-Mansfield Agitation Inventory; CMAI-IPA, Cohen-Mansfield Agitation Inventory-International Psychogeriatric Association; C-SRSS, Columbia-Suicide Severity Rating Scale; EEG, electrocardiogram; IPA, International Psychogeriatric Association; IPSS, International Prostate Symptom Score; KarXT, xanone/mecloprid/tropium chloride; NPI, Neuropsychiatric Inventory; NPI-NH, Neuropsychiatric Inventory-Nursing Home; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- The ADAGIO-1 and ADAGIO-2 trials are expected to enroll approximately 426 participants each worldwide (**Figure 3**)
 - Enrollment began in July 2025 and is expected to complete in 2028

Figure 3. Countries with sites participating in ADAGIO-1 and/or ADAGIO-2^{a,b}



Conclusions

- There is an unmet need for treatments that effectively improve symptoms of agitation associated with AD
- ADAGIO-1 and ADAGIO-2 are identical, pivotal, randomized, double-blind, placebo-controlled, parallel group, phase 3 trials evaluating the efficacy and safety of KarXT for the treatment of agitation associated with AD
- Participant enrollment began in July 2025; primary completion is projected for 2028
- Pending ADAGIO program efficacy and safety results, KarXT has the potential to be a novel treatment for agitation associated with AD with a unique mechanism of action based on muscarinic receptor agonism

References

1. Halpern R, et al. *Int J Geriatr Psychiatry*. 2019;34:420-431.
2. Zabodne LB, et al. *Am J Geriatr Psychiatry*. 2017;25:130-140.
3. Livingston G, et al. *BJPsych Open*. 2017;3:171-178.
4. Schein J, et al. *J Alzheimers Dis*. 2022;88:663-677.
5. Grossberg G, et al. *J Med Econ*. 2024;27:99-108.
6. Cummings JL, et al. *CNS Spectr*. 2024;23:1-10.
7. Hung S-Y and Fu W-M. *J Biomed Sci*. 2017;24:47.
8. Reeves S, et al. *Neurology*. 2009;72:528-534.
9. Bodick NC, et al. *Arch Neurol*. 1997;54:465-473.
10. Breier A, et al. *Psychopharmacology (Berl)*. 2023;240:1191-1198.
11. Yeung PP, et al. *J Clin Psychiatry*. 2025;86:24m15668.

Acknowledgments

- These trials were supported by Bristol Myers Squibb
- Writing and editorial assistance was provided by Deja Scott-Shemon, MPH, of Peloton Advantage, LLC, an OPEN Health company, funded by Bristol Myers Squibb
- The authors would like to acknowledge Niladri Roy Chowdhury, Lisa MacPeck, Katie Gore, Mackenzie Minogue, and Anamaria Jorga of Bristol Myers Squibb for assistance with study support, trial design, and execution
- The authors thank the participants and families engaging in these trials as well as the clinical study teams

Disclosures

- **YS, FS, and RS:** Employees of Bristol Myers Squibb
- **IR:** Employee of MapLight Therapeutics; former employee of Bristol Myers Squibb
- **RM:** Employee of Bristol Myers Squibb at the time of study initiation
- **GG:** Consultant for Axsome, Biogen, BioXcel, Bristol Myers Squibb, Eisai, Karuna, Lundbeck, MapLight, Otsuka, and Takeda; Research support for NIA and Functional Neuroimaging; Safety monitoring committee for Anavex, Merck, Newron, Oligomerix, and Quince; Speakers bureau for Biogen, Eisai, and Otsuka

Scientific Content on Demand

