Health Technology Briefing
April 2026

Xanomeline tartrate-trospium chloride for treating psychosis associated with Alzheimer's disease

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 35845	NICE ID: Not available	UKPS ID: 675219

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Xanomeline tartrate-trospium chloride is being developed for the treatment of psychosis associated with Alzheimer's disease (AD). AD is an illness that damages a person's brain. AD is the most common cause of dementia, which affects memory and thinking. The symptoms of AD develop gradually over many years and eventually become more severe, affecting multiple brain functions. Over half of people with AD will experience psychotic symptoms during their illness. Psychosis is defined by the presence of delusions, delusional misidentification and hallucinations. The traditional antipsychotic medications, commonly prescribed to manage these symptoms, cause significant side effects with limited efficacy, requiring novel therapeutic agents that can overcome this challenge.

Xanomeline tartrate-trospium chloride is a combination of two medicines given orally as a single capsule. It works in a way that aims to improve both negative and positive symptoms. If licensed, xanomeline- tartrate-trospium chloride will offer an additional treatment option for psychosis associated with AD.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

Treatment of psychosis associated with Alzheimer's disease (AD).[1]

Technology

Description

Xanomeline tartrate-trospium chloride (KarXT, Cobenfy) is an investigational treatment that combines xanomeline (an M1/M4 muscarinic receptor agonist) and trospium chloride (a peripherally restricted muscarinic antagonist) to target central nervous system pathways while minimising peripheral side effects, modulating cholinergic neurotransmission to reduce psychosis symptoms in AD.[2] Pharmacological activation of muscarinic receptors M1 and M4 may represent a target for treatment of psychiatric symptoms, including psychosis and agitation, associated with AD.[3]

In the phase III trials (ADEPT-1, NCT05511363; ADEPT-2, NCT06126224; ADEPT-3, NCT05980949; ADEPT-4, NCT06585787; ADEPT-5, NCT06947941), participants will receive a xanomeline tartrate-trospium chloride capsule three times daily (20 mg/2 mg, 30 mg/3 mg, 40 mg/4 mg, 50 mg/5 mg, 66.7 mg/6.67 mg).[1]

Key Innovation

Acute psychotic symptoms like delusions and hallucinations are of major concern while treating patients with AD psychosis, primarily impacting their daily life functioning and quality of life. Conventional treatments target dopamine receptors as their mechanism of action, which results in undesirable side effects like extrapyramidal symptoms, limiting their use and increasing the chances of patients' noncompliance with medication.[2] By mitigating peripheral side effects, trospium chloride enhances the tolerability and safety of xanomeline tartrate, enabling its central therapeutic actions.[4]

If licensed, xanomeline tartrate-trospium chloride will offer an additional treatment option for people with psychosis associated with AD who currently have few well-tolerated effective therapies available.

Regulatory & Development Status

Xanomeline tartrate-trospium chloride does not currently have Marketing Authorisation in the EU/UK for any indication.

Xanomeline tartrate-trospium chloride is in phase III/II clinical development for:[5,6]

- autism-related irritability
- schizophrenia
- manic episodes in bipolar-1 disorder
- agitation associated with AD
- cognitive impairment associated with AD

Patient Group

Disease Area and Clinical Need

AD is the most common cause of dementia in the UK. Dementia is the name for a group of symptoms associated with an ongoing decline of brain functioning. It can affect memory, thinking skills and other mental abilities. AD is a progressive condition, meaning the symptoms develop gradually over many years

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and eventually become more severe.[7] While AD is commonly thought of as a memory disorder, behavioural and psychological symptoms of dementia are nearly universal and include psychotic symptoms. Over half of people with AD will experience psychotic symptoms during their illness. Psychosis is defined by the presence of delusions, delusional misidentification and hallucinations. Psychotic symptoms are frequently distressing to the individual and their caregivers and associated with poorer disease outcomes.[8] The heritability estimates of psychosis in AD from a major international genome-wide association study ranged from 18% to 31% depending on the method used. This study also reported the first genome-wide significant risk loci for psychosis in AD, which were located in ENPP6 and SUMF1.[9,10]

A systematic review reported psychosis in 41% of people with AD.[10,11] AD makes up 60-80% of the 1 million dementia cases in the UK.[12] In England (2024-25), there were 10,956 finished consultant episodes (FCE) and 4,170 admissions for AD (ICD-10 code G30), which resulted in 167 day cases and 139,694 FCE bed days.[13]

Recommended Treatment Options

There is no treatment option recommended by the National Institute for Health and Care Excellence (NICE) for psychosis associated with AD.

For first episode psychosis, NICE recommends oral antipsychotic medication in conjunction with psychological interventions (family intervention and individual cognitive behavioural therapy).[14]

Clinical Trial Information

Trial	**ADEPT-1, NCT05511363, EudraCT 2022-001515-10**; A Phase 3, Randomized, Double-Blind, Placebo-Controlled Relapse Prevention Study to Evaluate the Safety and Efficacy of KarXT for the Treatment of Psychosis Associated With Alzheimer's Disease **Phase III** – Recruiting **Locations:** Eight EU countries, UK, USA and Serbia **Primary completion date:** October 2026
Trial Design	Randomised, single group assignment, quadruple masking
Population	N (estimated)=410 subjects with psychosis associated with Alzheimer's disease; aged 55 to 90 years old
Intervention(s)	Xanomeline and trospium chloride capsules
Comparator(s)	Placebo capsules
Outcome(s)	Time from randomisation to relapse during the 38-week study [Time frame: week 38] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

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Trial	**ADEPT-2,** NCT06126224; A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of KarXT for the Treatment of Psychosis Associated With Alzheimer's Disease **Phase III** – Active, not recruiting **Locations:** 4 EU countries, USA and other countries **Primary completion date:** December 2026
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N (estimated)=500; subjects with psychosis associated with Alzheimer's disease; aged 55 to 90 years old
Intervention(s)	Xanomeline and trospium chloride capsules
Comparator(s)	Placebo capsules
Outcome(s)	Change from baseline to end of treatment in the neuropsychiatric inventory-clinician: hallucinations and delusions (NPI-C: H+D) score [Time frame: baseline and end of treatment (up to 14 weeks)] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**ADEPT-4,** NCT06585787; A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of KarXT for the Treatment of Psychosis Associated With Alzheimer's Disease **Phase III** – Recruiting **Locations:** Thirteen EU countries, USA and other countries **Primary completion date:** September 2026
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N (estimated)=406; subjects with psychosis associated with Alzheimer's disease; aged 55 to 90 years old
Intervention(s)	Xanomeline and trospium chloride
Comparator(s)	Placebo
Outcome(s)	Change from baseline in NPI-C: H+D score [Time frame: up to week 14] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

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Trial	**ADEPT-3,** NCT05980949; Open-Label Extension Study to Assess the Long-Term Safety and Tolerability of KarXT in Subjects With Psychosis Associated With Alzheimer's Disease **Phase III** – Recruiting **Locations:** Fourteen EU countries, UK, USA, Canada and other countries **Primary completion date:** September 2027
Trial Design	Single group assignment, open label
Population	N (estimated)=800; subjects with psychosis associated with Alzheimer's disease; aged 55 to 90 years old, who had completed study CN012-0026, CN012-0027 or CN012-0056
Intervention(s)	Xanomeline and trospium chloride capsules
Comparator(s)	-
Outcome(s)	Incidence of treatment-emergent adverse events (TEAEs) [Time frame: from initial dose through 14 days after the final dose (up to 54 weeks)] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**ADEPT-5,** NCT06947941; A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Evaluate the Safety and Efficacy of KarXT + KarX-EC for the Treatment of Psychosis Associated With Alzheimer's Disease **Phase III** – Not yet recruiting **Location(s):** Not available **Primary completion date:** September 2027
Trial Design	Randomised, parallel assignment, quadruple masking
Population	N (estimated)=1046; subjects with psychosis associated with Alzheimer's disease; aged 55 to 90 years old
Intervention(s)	• Xanomeline and trospium chloride • Xanomeline enteric-coated
Comparator(s)	Matching placebo
Outcome(s)	Change from baseline in NPI-C: H+D score [Time frame: up to week 12] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

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The cost of xanomeline tartrate-trospium chloride is not yet known.

Relevant Guidance

NICE Guidance

- NICE guideline. Rehabilitation for adults with complex psychosis. [NG181]. August 2020.
- NICE clinical guideline. Dementia: assessment, management and support for people living with dementia and their carers (NG97). June 2018.
- NICE clinical guideline. Psychosis and schizophrenia in adults: prevention and management (CG178). March 2014.
- NICE quality standard. Dementia (QS184). June 2019.
- NICE Quality standard. Psychosis and schizophrenia in adults. [QS80]. February 2015.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. Improving the physical health of people living with severe mental illness: Guidance for integrated care systems. Publishing reference: B1955. January 2024.
- NHS England. Implementing the early intervention in psychosis access and waiting time standard. Version 3. Publication reference: PR1954. February 2023.
- NHS England. Mental Health Implementation Plan 2019/20 - 2023/24. Publishing approval reference: 000830. July 2019.
- NHS England. Treatment of psychosis and schizophrenia algorithm. Version 2. Guideline number: 726FM. March 2018.

Other Guidance

- The American Psychiatric Association. Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients with Dementia. 2016.[15]
- Alzheimer's Society. Optimising treatment and care for people with behavioural and psychological symptoms of dementia: A best practice guide for health and social care professionals. 2011.[16]

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