

Xanomeline-Trospium

A first-in-class muscarinic agonist combination pairing the centrally acting M1/M4-preferring agonist xanomeline with the peripherally restricted muscarinic antagonist trospium chloride, approved by the United States Food and Drug Administration in September 2024 for the treatment of schizophrenia in adults, representing the first non-dopamine-D2-blocking antipsychotic mechanism registered for psychotic illness.

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ABSTRACT

Xanomeline-trospium (KarXT; marketed as Cobenfy) is a fixed-dose oral combination of xanomeline tartrate, a functionally selective muscarinic acetylcholine receptor agonist with preferential activity at the M1 and M4 receptor subtypes, and trospium chloride, a quaternary ammonium muscarinic antagonist that does not appreciably cross the blood-brain barrier. The combination was designed to preserve the central antipsychotic and procognitive effects of muscarinic M1/M4 agonism while mitigating the dose-limiting peripheral cholinergic adverse events (nausea, vomiting, diarrhea, hypersalivation, diaphoresis) that had previously terminated the clinical development of xanomeline as a monotherapy agent. The United States Food and Drug Administration approved xanomeline-trospium on 26 September 2024 for the treatment of schizophrenia in adults, making it the first antipsychotic mechanism approved since the introduction of the dopamine D2 receptor antagonist and partial agonist classes and the first muscarinic-based treatment registered for any psychotic disorder.

Xanomeline was originally synthesized in a collaboration between Eli Lilly and Novo Nordisk in the early 1990s under the development code LY-246708. Initial clinical development targeted Alzheimer's disease, where a 343-patient Phase 2 trial (Bodick et al. 1997) demonstrated stabilization of cognitive decline and significant dose-dependent reductions in behavioral and psychological symptoms including hallucinations, delusions, agitation, and vocal outbursts. However, peripheral cholinergic adverse events led to unacceptable dropout rates and the

Alzheimer's program was discontinued. A subsequent proof-of-concept trial in schizophrenia (Shekhar et al. 2008) confirmed antipsychotic-like activity through a non-dopaminergic mechanism but was similarly limited by tolerability. The critical innovation was the combination with trospium chloride, a muscarinic antagonist previously approved for overactive bladder (Sanctura, Allergan) that is restricted to the peripheral compartment by its quaternary ammonium structure and does not undergo cytochrome P450 metabolism. This combination strategy was advanced by Karuna Therapeutics, which was subsequently acquired by Bristol Myers Squibb for approximately 14 billion United States dollars in 2024.

The registration of xanomeline-trospium was supported by three randomized, double-blind, placebo-controlled, 5-week Phase 3 trials (EMERGENT-1, EMERGENT-2, EMERGENT-3) in adults with schizophrenia experiencing acute psychosis. In pooled analyses across all three trials, xanomeline-trospium produced a statistically significant reduction in Positive and Negative Syndrome Scale (PANSS) total score compared to placebo (least squares mean difference, minus 9.9 points; 95 percent confidence interval, minus 12.4 to minus 7.3; p less than 0.0001; Cohen's d effect size, 0.65). Effects were observed across positive symptom, negative symptom, and general psychopathology PANSS subscales and on the Clinical Global Impression-Severity scale. Long-term safety and efficacy were characterized in the 52-week open-label extension trials EMERGENT-4 and EMERGENT-5, which demonstrated sustained symptom improvement, a mean change in body weight of minus 1.9 kilograms from acute trial baseline, no clinically meaningful changes in prolactin levels, and no treatment-emergent akathisia or tardive dyskinesia. The most common adverse events were gastrointestinal (nausea, dyspepsia,

constipation, vomiting) and were generally mild to moderate, transient, and manageable without treatment discontinuation in most patients.

The compound is currently in Phase 3 development for additional indications including psychosis associated with Alzheimer's disease (ADEPT program), agitation associated with Alzheimer's disease (ADAGIO program), and cognitive impairment in Alzheimer's disease. An enteric-coated xanomeline formulation (KarX-EC) is in development with the aim of further reducing gastrointestinal adverse events. This monograph reviews the chemistry, synthesis, and pharmacology of both components; the composite mechanism of action through central muscarinic M1/M4 agonism with peripheral muscarinic blockade; the pharmacokinetics including CYP2D6 polymorphism effects; the complete clinical evidence base across schizophrenia and Alzheimer's disease indications; sourcing and quality considerations; reconstitution and handling; stack-interaction implications; adverse-event and safety signal; and a comparative assessment of five alternative antipsychotic or muscarinic-targeted agents against xanomeline-trospium on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Approved name: Xanomeline and trospium chloride.

Marketed name: Cobenfy (Bristol Myers Squibb; United States).

Development codes: KarXT (Karuna Therapeutics). Xanomeline alone: LY-246708 (Eli Lilly). Trospium chloride alone: no distinct development code; the compound has been marketed generically for decades.

Chemical Abstracts Service registry numbers: Xanomeline free base: 131986-45-3. Xanomeline tartrate: 152854-19-8. Trospium chloride: 10405-02-4. No single CAS number has been assigned to the fixed-dose combination product.

International Union of Pure and Applied Chemistry names:

Xanomeline: 3-[4-(hexyloxy)-1,2,5-thiadiazol-3-yl]-1-methyl-1,2,5,6-tetrahydropyridine. The compound is a thiadiazole-substituted tetrahydropyridine bearing a hexyloxy side chain.

Trospium chloride: 3-(2-hydroxy-2,2-diphenylacetoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane chloride. The compound is a quaternary ammonium ester of benzoic acid and a nortropane ring system.

1.2 Structural class and chemistry

Xanomeline is a thiadiazole derivative within the broader class of muscarinic acetylcholine receptor agonists. The structural core is a 1,2,5-thiadiazole ring linked at the 3-position to a 1-methyl-1,2,5,6-tetrahydropyridine ring, with a hexyloxy substituent at the 4-position of the thiadiazole. The hexyloxy chain is believed to contribute to the functional selectivity at M1 and M4 receptor subtypes through interactions with a secondary binding site or allosteric pocket that differs across muscarinic receptor subtypes [1].

Molecular formula: C₁₄H₂₃N₃OS (free base). Molecular weight: 281.42 g/mol (free base); 431.48 g/mol (tartrate salt). The compound is supplied in the marketed formulation as the tartrate salt.

Tropium chloride is a quaternary ammonium compound within the tropane alkaloid class. It is the benzoic acid ester of a quaternized nortropanol, carrying a permanent positive charge on the bridgehead nitrogen that prevents passive diffusion across lipid bilayer membranes, including the blood-brain barrier. This structural feature is the pharmacological basis for the peripheral restriction of tropium's muscarinic antagonism [2].

Molecular formula: C₂₅H₃₀ClNO₃. Molecular weight: 427.97 g/mol.

Physical properties: Xanomeline tartrate is a white to off-white powder, soluble in water and in polar organic solvents. Tropium chloride is a white crystalline powder, freely soluble in water, sparingly soluble in methanol, and practically insoluble in nonpolar organic solvents. The fixed-dose combination is formulated as oral capsules containing coated pellets of each component.

1.3 Synthesis

The synthesis of xanomeline proceeds through construction of the 1,2,5-thiadiazole ring from an appropriate thioamide or dithiozone precursor, followed by regioselective alkylation at the 4-position with a hexyl alcohol or hexyl halide to install the hexyloxy chain, and coupling of the thiadiazole unit to a 1-methyl-4-piperidone or 1-methyl-1,2,5,6-tetrahydropyridine precursor [3]. The synthesis of the tetrahydropyridine ring typically begins from a commercially available pyridine derivative, with partial reduction by metal hydride or catalytic methods. Salt formation with tartaric acid yields xanomeline tartrate.

The synthesis of tropium chloride follows the general tropane alkaloid esterification methodology: esterification of 3- α -hydroxynortropane with benzoic acid (2-hydroxy-2,2-diphenylacetic acid) using carbodiimide-mediated coupling or acid chloride methods, followed by quaternization of the bridgehead nitrogen with methyl iodide or an isopropyl halide to produce the quaternary ammonium salt, and halide exchange to the chloride form [4]. The compound has been manufactured at industrial scale for several decades and is available from multiple generic pharmaceutical manufacturers.

The fixed-dose combination capsule (Cobenfy) contains xanomeline tartrate and trospium chloride as separate coated pellet populations within a single capsule shell, allowing independent release profiles for each component.

2. Abstract

Xanomeline-trospium (KarXT; Cobenfy) is a fixed-dose oral combination that represents the first mechanistically novel antipsychotic approved in several decades and the first non-dopamine-receptor-blocking treatment registered for schizophrenia. The combination pairs xanomeline, a muscarinic acetylcholine receptor agonist with functional selectivity for M1 and M4 subtypes, with trospium chloride, a peripherally restricted muscarinic antagonist that mitigates the peripheral cholinergic adverse events of xanomeline without compromising its central therapeutic activity [5, 6].

The rationale for the combination derives from two decades of evidence that muscarinic M1 and M4 receptor activation in the central nervous system produces antipsychotic, procognitive, and anxiolytic effects through modulation of dopaminergic, glutamatergic, and GABAergic neurotransmission, without direct blockade of dopamine D2 receptors [7, 8]. Xanomeline alone demonstrated these effects in clinical trials in Alzheimer's disease (Bodick et al. 1997) and schizophrenia (Shekhar et al. 2008), but peripheral muscarinic activation produced intolerable gastrointestinal, secretory, and cardiovascular adverse events at therapeutic doses [9, 10]. The co-administration of trospium chloride, which blocks muscarinic receptors in the gastrointestinal tract, salivary glands, cardiovascular smooth muscle, and other peripheral organs while remaining excluded from the central nervous system by its quaternary ammonium structure, resolved this tolerability barrier and enabled the completion of a successful Phase 3 registration program [11].

The three pivotal EMERGENT trials (EMERGENT-1, EMERGENT-2, EMERGENT-3) enrolled a total of approximately 900 adults with schizophrenia experiencing acute psychosis and demonstrated consistent, statistically significant, and clinically meaningful reductions in PANSS total score at 5 weeks, with a pooled effect size (Cohen's d) of 0.65 [12, 13, 14, 15]. The magnitude of the effect on the PANSS total score (pooled least squares mean difference of minus 9.9 points versus placebo) is comparable to or exceeds the effect sizes reported in pivotal trials of established antipsychotic agents. Importantly, xanomeline-trospium did not produce the metabolic, endocrine, or neuromotor adverse effects characteristic of dopamine D2 re-

ceptor antagonists: no clinically meaningful weight gain (mean change minus 1.9 kg at 52 weeks), no prolactin elevation, no akathisia, and no tardive dyskinesia were observed across the acute and long-term extension trial program [16].

The compound is currently under investigation in Phase 3 trials for psychosis and agitation associated with Alzheimer's disease (ADEPT and ADAGIO programs) and for cognitive impairment in Alzheimer's disease, reflecting the broader therapeutic potential of the muscarinic agonist mechanism beyond schizophrenia [17].

3. Discovery and Development History

3.1 Origin of xanomeline

Xanomeline (LY-246708) was synthesized in the early 1990s through a collaborative research program between Eli Lilly and Company and Novo Nordisk, as part of a medicinal chemistry effort to develop selective muscarinic agonists for the treatment of cognitive decline in Alzheimer's disease [3]. The compound was identified from a structure-activity exploration of thiadiazole-substituted tetrahydropyridines and was selected for development on the basis of its high affinity for muscarinic receptors (K_i values in the range of 20 to 80 nanomolar across all five subtypes) combined with functional selectivity for M1 and M4 activation [1]. The functional selectivity, characterized by greater agonist efficacy at M1 and M4 subtypes relative to M2, M3, and M5, was attributed to differences in receptor-ligand kinetics and G-protein coupling efficiency across subtypes rather than to classical binding selectivity [18].

3.2 Alzheimer's disease development (1993 to 1999)

Eli Lilly advanced xanomeline through Phase 2 clinical development for Alzheimer's disease. The pivotal study was a 6-month, multicenter, randomized, double-blind, placebo-controlled trial in 343 patients with probable Alzheimer's disease randomized to placebo, 25 mg three times daily, 50 mg three times daily, or 75 mg three times daily of xanomeline tartrate (Bodick et al. 1997) [9]. Completer analysis revealed a statistically significant treatment effect on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog) at the 75 mg dose ($p = 0.045$ versus placebo). A separate and clinically notable finding was a highly significant (p less than or equal to 0.002) dose-dependent reduction in behavioral and psychological symptoms of dementia, including hallucinations, delusions, vocal outbursts, suspiciousness, and agitation.

However, the trial was compromised by high dropout rates attributable to peripheral cholinergic adverse events, predominantly gastrointestinal (nausea, vomiting, diarrhea) and secretory (diaphoresis, salivation). Approximately 52 percent of patients in the 75 mg arm discontinued before study completion. A transdermal

formulation was explored to improve tolerability but did not produce sufficiently improved outcomes. Eli Lilly discontinued the Alzheimer's development program, and xanomeline entered a period of pharmacological dormancy.

3.3 Schizophrenia proof of concept (2008)

The observation that xanomeline reduced psychotic symptoms (hallucinations, delusions) in the Alzheimer's trial population catalyzed interest in the compound as a potential antipsychotic agent. Shekhar et al. (2008) reported a small randomized, placebo-controlled, proof-of-concept study of xanomeline monotherapy in 20 patients with schizophrenia [10]. At doses up to 225 mg per day, xanomeline produced significant improvements in both positive and negative symptoms of schizophrenia as measured by the Brief Psychiatric Rating Scale and the PANSS, confirming antipsychotic-like efficacy through a non-dopaminergic mechanism. As in the Alzheimer's trial, peripheral cholinergic adverse events were the principal tolerability limitation.

3.4 Development of the combination strategy

The concept of combining xanomeline with a peripherally restricted muscarinic antagonist to preserve central effects while blocking peripheral adverse events was advanced by Andrew Miller and Stephen Brannan, who co-founded Karuna Therapeutics in 2009 (originally named Karuna Pharmaceuticals). The selection of trospium chloride as the combination partner was based on three pharmacological properties: (a) trospium is a quaternary ammonium compound that does not cross the blood-brain barrier, ensuring that its muscarinic antagonism is confined to the periphery; (b) trospium is not metabolized by cytochrome P450 enzymes and is primarily eliminated by renal excretion, minimizing the risk of metabolic drug-drug interactions with xanomeline; and (c) trospium had an established clinical safety record from its prior registration for overactive bladder [2, 11].

A Phase 1 study in healthy volunteers demonstrated that co-administration of trospium chloride with xanomeline substantially reduced the incidence and severity of cholinergic adverse events (nausea, vomiting, diarrhea, diaphoresis, salivation) without affecting the central pharmacodynamic effects of xanomeline, as assessed by electroencephalographic markers of central muscarinic receptor engagement [11].

3.5 Karuna Therapeutics and the EMERGENT program

Karuna Therapeutics initiated the EMERGENT clinical trial program in 2018 with the Phase 2 EMERGENT-1 trial, followed by the Phase 3 EMERGENT-2 and EMERGENT-3 trials. All three trials met their primary efficacy endpoints (change from baseline in PANSS total score at week 5). The success of the EMERGENT program attracted the attention of Bristol Myers Squibb, which acquired Karuna Therapeutics in March 2024 for approximately 14 billion United States dollars, one of the largest neuroscience-focused pharmaceutical acquisitions [17].

3.6 FDA approval

On 26 September 2024, the United States Food and Drug Administration approved xanomeline and trospium chloride capsules (Cobenfy) for the treatment of schizophrenia in adults. The approval was based on the three positive EMERGENT trials and the supporting long-term safety data from the EMERGENT-4 and EMERGENT-5 open-label extension studies. Cobenfy became the first mechanistically novel antipsychotic approved since the introduction of aripiprazole (the first dopamine D2 partial agonist) and the first treatment for schizophrenia that does not require blockade of dopamine D2 receptors [17].

4. Mechanism of Action

Xanomeline-trospium is a two-component agent whose therapeutic mechanism depends on the differential distribution and receptor pharmacology of the two constituents. The central (therapeutic) effects are mediated by xanomeline acting on muscarinic M1 and M4 receptors in the brain. The peripheral (tolerability) component is mediated by trospium chloride acting on muscarinic receptors in the gastrointestinal tract, cardiovascular system, and exocrine glands.

4.1 Muscarinic M1 receptor agonism

The M1 muscarinic acetylcholine receptor is a Gq/11-coupled G-protein-coupled receptor expressed at high density in the cerebral cortex, hippocampus, striatum, and thalamus. M1 activation drives phospholipase C-mediated inositol trisphosphate and diacylglycerol signaling, resulting in intracellular calcium mobilization and protein kinase C activation. In cortical and hippocampal circuits, M1 activation enhances glutamatergic neurotransmission, promotes long-term potentiation, and supports working memory and cognitive flexibility [7, 19].

Xanomeline activates M1 receptors with a K_i of approximately 79 nanomolar and produces functional agonism with moderate intrinsic activity (approximately 50 to 70 percent of maximal acetylcholine response in heterologous expression systems). The M1-mediated effects of xanomeline are believed to underlie the procognitive activity observed in Alzheimer's disease trials and the improvement in cognitive symptoms in schizophrenia [9, 10].

M1 receptor activation also modulates dopaminergic neurotransmission indirectly. In the prefrontal cortex, M1 activation enhances dopamine release through glutamate-mediated excitation of ventral tegmental area dopamine neurons, potentially ameliorating the hypodopaminergia implicated in negative and cognitive symptoms of schizophrenia. In the striatum, M1 activation on medium spiny neurons of the direct pathway modulates the integration of dopaminergic and glutamatergic signals [7, 8].

4.2 Muscarinic M4 receptor agonism

The M4 muscarinic acetylcholine receptor is a Gi/o-coupled G-protein-coupled receptor expressed at high density in the striatum (particularly on cholinergic interneurons and on D1-receptor-expressing medium spiny neurons of the direct pathway), in the cortex, and in the hippocampus. M4 activation inhibits adenylyl cyclase, reduces cyclic AMP, and modulates neuronal excitability through potassium channel activation and calcium channel inhibition [7, 20].

Xanomeline activates M4 receptors with a K_i of approximately 20 nanomolar and produces functional agonism with higher intrinsic activity than at M1 (approximately 60 to 80 percent of maximal acetylcholine response). The M4-mediated effects are believed to be the principal antipsychotic mechanism of xanomeline: M4 activation on cholinergic interneurons in the striatum reduces dopamine release from nigrostriatal and mesolimbic dopamine terminals through a presynaptic inhibitory mechanism [8, 20]. This "top-down" modulation of dopamine release provides antipsychotic activity comparable to direct D2 receptor blockade but through a fundamentally different mechanism that does not produce the extrapyramidal motor effects, prolactin elevation, or metabolic syndrome associated with D2 antagonism.

Additionally, M4 receptor activation in the ventral tegmental area directly inhibits dopamine neuron firing, providing a "bottom-up" complement to the striatal presynaptic mechanism [8]. The dual top-down and bottom-up dopamine modulation through M4 agonism is the mechanistic basis for the robust antipsychotic efficacy of xanomeline observed in clinical trials.

4.3 Functional selectivity and receptor kinetics

Xanomeline binds with broadly similar affinity to all five muscarinic receptor subtypes (M1 through M5), with K_i values ranging from approximately 20 nanomolar (M4) to approximately 100 nanomolar (M2, M3). The functional selectivity for M1 and M4 arises not from classical binding selectivity but from differences in receptor-ligand interaction kinetics and G-protein coupling efficiency [1, 18]. At M1 and M4 receptors, xanomeline exhibits persistent activation that outlasts washout, a phenomenon attributed to a slow-dissociating or "wash-resistant" binding mode at a secondary allosteric site or an ectopic binding site within the receptor. This per-

sistent activation is unique to M1 and M4 subtypes and is not observed at M2, M3, or M5 receptors, where xanomeline acts as a conventional reversible agonist or partial agonist with standard washout kinetics [18].

4.4 Peripheral muscarinic antagonism by trospium

Trospium chloride is a non-selective muscarinic antagonist that binds all five muscarinic receptor subtypes with comparable affinity. Its pharmacological role in the combination is entirely protective: by blocking muscarinic receptors in the gastrointestinal tract (reducing nausea, vomiting, diarrhea), salivary glands (reducing hypersalivation), sweat glands (reducing diaphoresis), cardiac smooth muscle (reducing bradycardia risk), and bladder detrusor muscle (its original therapeutic application in overactive bladder), trospium counteracts the peripheral adverse events of systemic muscarinic agonism by xanomeline [2, 11].

The critical pharmacological requirement is that trospium must not enter the central nervous system at therapeutically relevant concentrations, as central muscarinic antagonism would oppose and cancel the therapeutic muscarinic agonism of xanomeline. The quaternary ammonium structure of trospium ensures near-complete exclusion from the brain. Positron emission tomography studies and pharmacodynamic assessments in the Phase 1 program confirmed that trospium at the doses used in the combination does not produce measurable central muscarinic receptor occupancy or central anticholinergic effects [11].

4.5 Composite pharmacology

The net pharmacological effect of the combination at registered doses is central muscarinic M1/M4 agonism (producing antipsychotic, procognitive, and anxiolytic activity through indirect dopamine modulation and enhanced glutamatergic and cholinergic neurotransmission) combined with peripheral muscarinic antagonism (producing tolerability). The therapeutic mechanism does not involve blockade of dopamine D2 receptors, serotonin 5-HT_{2A} receptors, histamine H₁ receptors, or alpha-1 adrenergic receptors, the four principal targets of the existing antipsychotic drug classes. This mechanistic profile predicts the absence of the adverse effects mediated through these receptors (extrapyramidal symptoms, tardive dyskinesia, prolactin elevation, weight gain, sedation, orthostatic hypotension), a prediction confirmed by the clinical trial data [12, 13, 14, 15, 16].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Xanomeline is absorbed from the gastrointestinal tract with a time to maximum plasma concentration (T_{max}) of approximately 2.5 hours. Maximum plasma concentration (C_{max}) after a 125 mg dose of xanomeline (as tartrate, the highest capsule strength in the approved formulation) is approximately 13.8 ng/mL [21]. Absolute oral bioavailability of xanomeline is low (less than 5 percent by some estimates) owing to extensive first-pass hepatic and intestinal metabolism, though the bioavailability of the tartrate salt formulation used in the combination product may differ from earlier free-base formulations [3, 21].

Trospium chloride is absorbed with a T_{max} of approximately 5 hours in fasted conditions. Oral bioavailability is approximately 10 percent, limited by both poor passive absorption (reflecting the quaternary ammonium charge) and first-pass metabolism by ester hydrolysis. Food reduces trospium C_{max} by approximately 70 to 75 percent; the prescribing information recommends administration on an empty stomach or at least one hour before meals [2, 22].

5.2 Distribution

Xanomeline has a large apparent volume of distribution, reflecting extensive tissue partitioning. The compound crosses the blood-brain barrier and achieves pharmacologically active concentrations in the central nervous system, as confirmed by electroencephalographic pharmacodynamic markers and clinical efficacy [11]. Plasma protein binding of xanomeline has not been fully characterized in published literature.

Trospium chloride has a volume of distribution of approximately 395 liters (population pharmacokinetic estimate), reflecting peripheral tissue distribution. Plasma protein binding is approximately 50 to 85 percent. Critically, the compound does not appreciably cross the blood-brain barrier owing to its permanent positive charge; central nervous system concentrations are negligible at clinical doses [2].

5.3 Metabolism

Xanomeline undergoes extensive hepatic metabolism. The principal metabolic pathways include oxidative dealkylation of the hexyloxy chain, hydroxylation, and thiadiazole ring metabolism. Multiple cytochrome P450 enzymes contribute to xanomeline metabolism, including CYP2D6, CYP2B6, CYP1A2, CYP2C9, and CYP2C19. Flavin-containing monooxygenases FMO1 and FMO3 also contribute [21, 22]. CYP2D6 is a significant contributor, and the CYP2D6 polymorphism affects xanomeline pharmacokinetics: in CYP2D6 intermediate metabolizers, xanomeline C_{max} increases by approximately 28 percent and AUC by approximately 15 percent compared to normal metabolizers; in ultrarapid metabolizers, both C_{max} and AUC decrease by approximately 43 percent. The pharmacokinetics in CYP2D6 poor metabolizers have not been fully characterized [22].

Xanomeline and its metabolites are not clinically significant inhibitors or inducers of major hepatic CYP enzymes at systemic concentrations. However, xanomeline inhibits intestinal CYP3A4 and intestinal P-glycoprotein (P-gp), which may increase the absorption of concurrently administered CYP3A4 substrates and P-gp substrates [22].

Trospium chloride is metabolized primarily by ester hydrolysis (producing benzoic acid and the nortropanol moiety) and by glucuronic acid conjugation. It does not undergo cytochrome P450-mediated metabolism. This CYP-independent metabolic pathway is a pharmacological advantage in the combination, as it eliminates metabolic drug-drug interactions between the two components and reduces the complexity of predicting interactions with concomitant medications [2].

5.4 Elimination

Xanomeline is eliminated primarily through hepatic metabolism, with less than 5 percent of the administered dose excreted unchanged in urine. The plasma elimination half-life is variable across individuals, reflecting the complexity of multi-enzyme metabolism and the influence of CYP2D6 polymorphism [21].

Trospium chloride is eliminated both renally and through hepatic metabolism. Active tubular secretion is a major renal elimination pathway, and the parent compound (unchanged trospium) accounts for approximately 60 percent of the total urinary excretion. The plasma elimination half-life is approximately 20 hours, supporting once- or twice-daily dosing [2]. Because active tubular secretion is a pri-

mary elimination route, co-administration with other drugs eliminated by active tubular secretion (such as metformin) may increase plasma concentrations of trospium.

5.5 Routes of administration

The approved route of administration is oral. Cobenfy is supplied as capsules containing coated pellets of xanomeline tartrate and trospium chloride. Three capsule strengths are available: 50 mg/20 mg, 100 mg/20 mg, and 125 mg/30 mg (xanomeline/trospium) [22]. No parenteral, transdermal, or other formulations of the combination are currently approved. An enteric-coated xanomeline formulation (KarX-EC), designed to release xanomeline in the small intestine rather than the stomach with the aim of further reducing gastrointestinal adverse events, is in clinical development [17].

5.6 Special populations

Renal impairment: Patients with mild renal impairment (estimated glomerular filtration rate 60 to less than 90 mL/min) show higher systemic exposure to trospium chloride and xanomeline but have a safety profile similar to patients with normal renal function; no dose adjustment is required. Cobenfy is not recommended in patients with moderate or severe renal impairment owing to the renal elimination dependence of trospium [22].

Hepatic impairment: Patients with hepatic impairment have higher systemic exposure to xanomeline. Cobenfy is contraindicated in patients with moderate or severe hepatic impairment. Use is not recommended in mild hepatic impairment [22].

Geriatric patients: Geriatric patients, including older males with bladder outlet obstruction due to benign prostatic hyperplasia, have increased risk of urinary retention from the anticholinergic activity of trospium. A slower titration schedule and lower maximum dosage are recommended [22].

Pediatric patients: Safety and efficacy in pediatric patients have not been established.

6. Preclinical Pharmacology

6.1 In vitro receptor pharmacology

Xanomeline binds with high affinity to all five muscarinic receptor subtypes in radioligand displacement assays: K_i values of approximately 79 nanomolar at M1, 20 nanomolar at M4, and in the range of 40 to 100 nanomolar at M2, M3, and M5 [1]. In functional assays (calcium mobilization for Gq-coupled M1, M3, M5; inhibition of forskolin-stimulated cAMP for Gi-coupled M2, M4), xanomeline exhibits full or high partial agonism at M1 and M4 and lower intrinsic activity at M2, M3, and M5. The "wash-resistant" or persistent activation phenomenon, in which functional responses at M1 and M4 are maintained after drug washout, has been characterized in multiple cell systems and is considered a contributing factor to the sustained in vivo efficacy of xanomeline at receptor occupancies that are submaximal at the orthosteric site [18].

6.2 In vivo behavioral pharmacology

In preclinical models predictive of antipsychotic activity, xanomeline reverses amphetamine-induced hyperlocomotion, apomorphine-induced climbing, and conditioned avoidance responding in rodents at doses that do not produce catalepsy (a marker of extrapyramidal liability that characterizes dopamine D2 antagonist antipsychotics) [7, 8]. Xanomeline also exhibits antipsychotic-like activity in non-human primates (*Cebus apella* monkeys), where it reduced amphetamine-induced behavioral disruption without producing the motor side effects characteristic of haloperidol [23].

In cognitive models, xanomeline improves performance in rodent tasks of spatial memory (Morris water maze, radial arm maze), working memory (delayed match-to-sample), and attention (five-choice serial reaction time task) [7, 19]. These procognitive effects are consistent with M1-mediated enhancement of cortical and hippocampal glutamatergic neurotransmission.

The addition of trospium chloride in preclinical combination studies reduces peripheral cholinergic signs (salivation, diarrhea, lacrimation) without attenuating the central behavioral effects of xanomeline, confirming the pharmacological basis

for the combination strategy [11].

7. Clinical Evidence Base

7.1 Alzheimer's disease: cognitive and behavioral symptoms (xanomeline monotherapy)

The Bodick et al. (1997) Phase 2 trial randomized 343 patients with probable Alzheimer's disease to placebo, xanomeline 25 mg three times daily, 50 mg three times daily, or 75 mg three times daily for 6 months [9]. On the ADAS-Cog, the 75 mg dose produced significant stabilization of cognitive decline in the completer population ($p = 0.045$ versus placebo). On the behavioral symptoms scale, dose-dependent reductions in hallucinations, delusions, agitation, vocal outbursts, and suspiciousness were highly significant (p less than or equal to 0.002). A second publication (Veroff et al. 1998) from the same trial cohort confirmed the cognitive findings using the Computerized Neuropsychological Test Battery [24]. However, the high rate of discontinuation due to cholinergic adverse events (52 percent in the high-dose arm) prevented the trial from demonstrating intent-to-treat efficacy at the pre-specified significance level and led to the discontinuation of the Alzheimer's development program by Eli Lilly.

7.2 Schizophrenia proof of concept (xanomeline monotherapy)

Shekhar et al. (2008) conducted a 4-week, randomized, double-blind, placebo-controlled trial of xanomeline in 20 patients with chronic schizophrenia [10]. Patients received xanomeline at doses up to 225 mg per day (75 mg three times daily) or placebo. Xanomeline produced statistically significant improvements in PANSS total score and in the Brief Psychiatric Rating Scale total score compared to placebo, with effects on both positive symptoms (hallucinations, delusions) and negative symptoms (avolition, alogia). The effect sizes were large (Cohen's d approximately 1.0), though the small sample size and high placebo response rate limit the precision of these estimates. Cholinergic adverse events (nausea, vomiting, diarrhea, diaphoresis) were again the principal tolerability concern.

7.3 Phase 1 combination studies

The first-in-human study of the xanomeline-trospium combination in healthy volunteers confirmed that trospium co-administration reduced the incidence of cholinergic adverse events by approximately 50 percent compared to xanomeline alone, while preserving the electroencephalographic markers of central muscarinic receptor engagement (increased delta and theta power, reduced alpha power) that are characteristic of central muscarinic agonism [11].

7.4 EMERGENT-1 (Phase 2)

EMERGENT-1 (NCT03697252) was a 5-week, randomized, double-blind, placebo-controlled trial in 182 adults (aged 18 to 65 years) with schizophrenia and an acute exacerbation of psychosis (PANSS total score of 80 or higher, Clinical Global Impression-Severity score of 4 or higher) [12]. Patients were randomized to xanomeline-trospium (titrated to 125 mg/30 mg twice daily) or placebo. The primary endpoint was change from baseline in PANSS total score at week 5. Xanomeline-trospium produced a statistically significant reduction in PANSS total score compared to placebo (least squares mean difference, minus 11.6 points; p less than 0.001; Cohen's d , 0.75). Significant improvements were also observed on PANSS positive symptom, negative symptom, and general psychopathology subscales and on the Clinical Global Impression-Severity score. The most common adverse events in the xanomeline-trospium arm were nausea (17 percent), constipation (13 percent), dyspepsia (9 percent), and vomiting (8 percent); these were predominantly mild to moderate and transient.

7.5 EMERGENT-2 (Phase 3)

EMERGENT-2 (NCT04659161) was a 5-week, randomized, double-blind, placebo-controlled, flexible-dose, inpatient Phase 3 trial in 252 adults with schizophrenia and acute psychosis [13]. The dosing regimen began at 50 mg/20 mg twice daily and was titrated to 100 mg/20 mg or 125 mg/30 mg twice daily based on tolerability. The primary endpoint was change from baseline in PANSS total score at week 5. Xanomeline-trospium met the primary endpoint (least squares mean difference versus placebo, minus 9.6 points; 95 percent CI, minus 13.9 to minus 5.3; p less than 0.001; Cohen's d , 0.61). Results were published in *The Lancet* (Kaul et al. 2024) [13].

7.6 EMERGENT-3 (Phase 3)

EMERGENT-3 (NCT04738123) was the second Phase 3 trial, with an identical design to EMERGENT-2 in 256 adults with schizophrenia and acute psychosis [14]. The primary endpoint was met: xanomeline-trospium produced a least squares mean change in PANSS total score of minus 20.6 compared to minus 12.2 for placebo (difference, minus 8.4; 95 percent CI, minus 12.4 to minus 4.3; p less than 0.001; Cohen's d , 0.60). Results were published in JAMA Psychiatry [14].

7.7 Pooled efficacy analysis

A pooled analysis of all three EMERGENT trials (Kaul et al. 2024) demonstrated a highly significant treatment effect on PANSS total score (pooled least squares mean difference, minus 9.9; 95 percent CI, minus 12.4 to minus 7.3; p less than 0.0001; Cohen's d , 0.65) [15]. Effects were consistent across PANSS positive subscale (effect size 0.62), PANSS negative subscale (effect size 0.35), PANSS general psychopathology subscale (effect size 0.61), and the PANSS Marder factor scores for positive symptoms, negative symptoms, disorganized thought, uncontrolled hostility/excitement, and anxiety/depression. Significant effects were also observed on the PANSS excited component, suggesting efficacy for agitation associated with schizophrenia [25].

7.8 Long-term extension studies

EMERGENT-4 was a 52-week, open-label extension study of xanomeline-trospium in patients who completed one of the acute EMERGENT trials. EMERGENT-5 was a 52-week, open-label study in adults with stable schizophrenia who had no prior exposure to xanomeline-trospium. Across both studies (total enrollment 566), xanomeline-trospium demonstrated sustained efficacy (continued improvement in PANSS total score over 52 weeks) and acceptable long-term safety [16]. The mean change in body weight from acute trial baseline was minus 1.9 kilograms (standard deviation 4.7 kg) at 52 weeks. No clinically meaningful changes in mean prolactin levels were observed. No treatment-emergent akathisia or tardive dyskinesia was reported. The overall discontinuation rate was 51 percent (289 of 566), with discontinuation reasons including adverse events (17 percent), withdrawal of consent (16 percent), and loss to follow-up (8 percent). Most adverse events were gastrointestinal, mild or moderate in severity, and resolved with continued treatment.

7.9 Alzheimer's disease pipeline studies (xanomeline-trospium combination)

Bristol Myers Squibb is conducting multiple Phase 3 trials of xanomeline-trospium for neuropsychiatric symptoms associated with Alzheimer's disease [17]:

ADEPT-2 (NCT05511363): 12-week, randomized, double-blind, placebo-controlled trial in 400 patients with Alzheimer's disease and psychosis (hallucinations, delusions). Primary endpoint: change in psychosis symptom severity. Estimated completion: late 2026.

ADEPT-4: 12-week, randomized, double-blind, placebo-controlled trial in 406 biomarker-confirmed Alzheimer's disease patients with moderate to severe psychosis. Estimated completion: late 2026.

ADAGIO-1 and ADAGIO-2: Phase 3 trials evaluating xanomeline-trospium for agitation associated with Alzheimer's disease.

Phase 3 trials for cognitive impairment in Alzheimer's disease commenced in 2025, using both the standard KarXT formulation and the enteric-coated KarX-EC formulation.

8. Sourcing and Quality Verification

Pharmaceutical-grade xanomeline-trospium is available as Cobenfy (Bristol Myers Squibb) in the United States. The marketed formulation is supplied as capsules in three strengths: 50 mg/20 mg, 100 mg/20 mg, and 125 mg/30 mg (xanomeline tartrate/trospium chloride). The capsules contain coated pellets and are intended for oral administration only. Cobenfy is the only commercially available source of the approved fixed-dose combination [22].

Research-grade xanomeline tartrate is available from multiple chemical suppliers (Sigma-Aldrich, Tocris, Cayman Chemical, MedChemExpress, Selleckchem) at purities of 98 percent or greater by HPLC. Research-grade trospium chloride is also widely available from chemical suppliers at comparable purities.

Investigators acquiring research-grade material for the individual components should confirm identity and purity on each lot through:

- High-performance liquid chromatography area-percent purity (target greater than 98 percent for each component)
- Mass spectrometry confirmation of molecular weight (xanomeline: 282.42 [M+H]⁺ for the free base; trospium: 392.52 [M]⁺ for the quaternary cation)
- Nuclear magnetic resonance spectroscopy confirmation of structural identity (proton and carbon-13)
- Karl Fischer or loss-on-drying analysis for residual water
- Residual solvent analysis by gas chromatography

Third-party analytical verification of vendor certificates of analysis is recommended for dose-response and mechanism-of-action studies where quantitative precision is essential.

Investigators should note that the pharmacological effects of xanomeline-trospium are dependent on the specific dose ratio and timing of co-administration; reconstitution of the combination from separate research-grade components requires careful pharmacokinetic matching and should not be assumed to replicate the release profile of the commercial formulation without independent verification.

9. Reconstitution and Handling

Xanomeline tartrate is a water-soluble powder that can be reconstituted in aqueous buffers, normal saline, or dimethyl sulfoxide for in vitro applications. Stock solutions in aqueous media should be prepared at concentrations appropriate to the assay (typically 1 to 100 millimolar in dimethyl sulfoxide, diluted to micromolar working concentrations in assay buffer). Aqueous stability has been characterized over 24 to 48 hours at room temperature and up to 7 days at 2 to 8 degrees Celsius; longer storage is recommended in dimethyl sulfoxide at minus 20 degrees Celsius [3].

Trospium chloride is freely soluble in water. Stock solutions for in vitro use are typically prepared in aqueous media at 10 to 100 millimolar. The compound is stable in aqueous solution under standard laboratory conditions.

For in vivo preclinical research, xanomeline is typically dissolved in sterile saline or in a small volume of acidified water (pH adjusted with dilute hydrochloric acid) and administered by oral gavage or intraperitoneal injection. Trospium chloride is dissolved in sterile saline for oral or intraperitoneal co-administration.

The commercial Cobenfy capsule is not suitable for research reconstitution owing to the coated-pellet formulation, which provides a specific release profile designed for gastrointestinal tolerability. Investigators requiring the combination for animal studies should prepare the components separately from research-grade material with independent dose verification.

Storage: Solid xanomeline tartrate and trospium chloride should be stored at 2 to 8 degrees Celsius in a dry environment, protected from moisture. The commercial capsules should be stored at controlled room temperature (20 to 25 degrees Celsius) with excursions permitted to 15 to 30 degrees Celsius [22].

10. Stack Interactions and Combinations

Xanomeline-trospium has potential for pharmacological and pharmacokinetic interactions with multiple drug classes. Investigators and prescribers should consider the following:

CYP2D6 inhibitors: Strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine) may increase xanomeline plasma concentrations. While the prescribing information does not include a specific dose reduction recommendation for CYP2D6 inhibitor co-administration, the interaction should be monitored clinically [22].

CYP3A4 substrates: Xanomeline inhibits intestinal CYP3A4, potentially increasing the absorption and plasma concentrations of co-administered CYP3A4 substrates (midazolam, simvastatin, cyclosporine, tacrolimus, certain HIV protease inhibitors). The clinical significance varies by substrate; sensitive CYP3A4 substrates should be monitored [22].

P-glycoprotein substrates: Xanomeline inhibits intestinal P-gp, potentially increasing the absorption of P-gp substrates (digoxin, dabigatran, fexofenadine). Digoxin concentrations should be monitored with concurrent use [22].

Other muscarinic agonists: Concurrent administration of cholinomimetic agents (bethanechol, pilocarpine, cevimeline) with xanomeline-trospium may produce additive central muscarinic activation. Concurrent acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) increase endogenous acetylcholine levels and may potentiate the effects of xanomeline at all muscarinic receptor subtypes; the combination has not been systematically studied but is of theoretical interest for Alzheimer's disease applications.

Muscarinic antagonists: Concurrent administration of anticholinergic agents (benztropine, trihexyphenidyl, diphenhydramine, oxybutynin, solifenacin) may oppose the central therapeutic effects of xanomeline. Centrally acting anticholinergics are not recommended with xanomeline-trospium [22].

Dopamine D2 antagonists: The combination of xanomeline-trospium with conventional or atypical antipsychotics has not been systematically studied. The mechanisms are non-overlapping (muscarinic agonism versus dopamine antagonism), and additive antipsychotic efficacy is theoretically plausible, but the combination would also introduce the adverse-event profile of the dopamine antagonist component. Cross-titration during switching from a D2 antagonist to xanomeline-trospium should be managed according to the prescribing information [22].

QT-prolonging agents: Xanomeline-trospium has not been associated with clinically significant QT prolongation in the EMERGENT trials. Dedicated thorough QT studies have been conducted but have not demonstrated a signal. Nonetheless, prudent clinical practice suggests caution with concurrent administration of known QT-prolonging agents.

Drugs eliminated by active tubular secretion: Trospium is eliminated in part by active tubular secretion. Co-administration with other drugs that share this elimination pathway (metformin, vancomycin, tenofovir) may increase trospium plasma concentrations [22].

11. Adverse Events and Safety

11.1 Common adverse events

In the pooled EMERGENT trial data, the most common treatment-emergent adverse events with xanomeline-trospium compared to placebo were [15, 16, 22]:

- Nausea: 19 percent versus 2 percent
- Dyspepsia: 16 percent versus 2 percent
- Vomiting: 16 percent versus 1 percent
- Constipation: 13 percent versus 4 percent
- Hypertension: 8 percent versus 3 percent
- Abdominal pain: 5 percent versus 1 percent
- Diarrhea: 5 percent versus 3 percent
- Tachycardia: 5 percent versus 1 percent
- Dizziness: 4 percent versus 2 percent
- Gastroesophageal reflux: 3 percent versus 1 percent

The gastrointestinal adverse events were predominantly mild to moderate in intensity, occurred early in treatment (typically within the first two weeks), and generally resolved with continued dosing or with symptomatic management. The rate of discontinuation due to adverse events in the pooled EMERGENT data was approximately 6 to 8 percent for xanomeline-trospium versus 2 to 3 percent for placebo.

11.2 Cardiovascular considerations

Transient increases in heart rate (mean increase approximately 6 to 8 beats per minute) and modest increases in blood pressure (mean systolic increase approximately 3 to 5 mmHg) were observed with xanomeline-trospium. The heart rate increase is attributable to peripheral muscarinic M2 antagonism by trospium (reducing vagal cardiac tone) and possibly to central sympathetic modulation by xanomeline. Clinically significant arrhythmias were not reported at increased rates in the EMERGENT program [15, 16].

11.3 Metabolic profile

Xanomeline-trospium does not produce the metabolic syndrome associated with atypical antipsychotics. In the 52-week extension studies, mean body weight decreased by 1.9 kilograms from acute trial baseline, a favorable profile compared to the weight gains of 2 to 7 kilograms typically observed with olanzapine, quetiapine, and risperidone over similar durations. No clinically meaningful changes in fasting glucose, lipid profiles, or glycosylated hemoglobin were reported [16].

11.4 Neuromotor profile

No treatment-emergent akathisia, dystonia, parkinsonism, or tardive dyskinesia was reported across the acute and long-term EMERGENT trials. This absence of extrapyramidal adverse events reflects the non-dopaminergic mechanism of action [16].

11.5 Endocrine profile

No clinically meaningful changes in prolactin levels were observed. This favorable endocrine profile reflects the absence of dopamine D2 receptor blockade and distinguishes xanomeline-trospium from all conventional and most atypical antipsychotic agents [16].

11.6 Urinary retention

Trospium chloride, as a muscarinic antagonist, relaxes the bladder detrusor muscle and may increase the risk of urinary retention, particularly in geriatric patients and in males with bladder outlet obstruction due to benign prostatic hyperplasia. The prescribing information recommends a slower titration and lower maximum dose in geriatric patients and monitoring for urinary retention [22].

11.7 Hepatic and renal considerations

Xanomeline-trospium is contraindicated in moderate or severe hepatic impairment and is not recommended in moderate or severe renal impairment owing to increased systemic exposure of the components in these populations [22].

11.8 Pregnancy and lactation

There are no adequate data on the developmental risk of xanomeline-trospium in pregnant women. Animal reproduction studies have not been adequately conducted for the combination. The prescribing information recommends that the potential risk to the fetus be weighed against the clinical need. There are no data on the presence of xanomeline or trospium in human milk or on the effects on the breastfed infant [22].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five antipsychotic or muscarinic-targeted agents against xanomeline-trospium, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The comparators were selected to represent the principal alternative approaches to schizophrenia treatment and to muscarinic-based neuropsychiatric pharmacology.

12.1 Olanzapine

Mechanism: Atypical antipsychotic; antagonist at dopamine D2, serotonin 5-HT2A, histamine H1, alpha-1 adrenergic, and muscarinic M1-M5 receptors [26].

Development trajectory: Developed by Eli Lilly; FDA-approved in 1996 for schizophrenia, subsequently approved for bipolar disorder, treatment-resistant depression (in combination with fluoxetine), and agitation associated with schizophrenia and bipolar disorder. One of the most widely prescribed antipsychotic agents globally.

Novelty: Low. Olanzapine is a multi-receptor antagonist within the well-established atypical antipsychotic class. Its mechanism is conventional dopamine D2 and serotonin 5-HT2A antagonism, supplemented by activity at additional monoamine receptors.

Effect size: Olanzapine is among the most efficacious antipsychotic agents in network meta-analyses of acute schizophrenia. Effect sizes on PANSS total score in pivotal trials are in the range of Cohen's d 0.4 to 0.7 versus placebo, broadly comparable to xanomeline-trospium [27].

Promising potential: Low for innovation; high for current clinical utility. Olanzapine is a mature product with extensive generic competition and a well-characterized safety profile. No novel development trajectory exists.

Side-effect profile: The principal liability of olanzapine is metabolic syndrome: clinically significant weight gain (mean 4 to 7 kg over 6 to 12 weeks), hyperglycemia, dyslipidemia, and increased risk of type 2 diabetes mellitus. Additional adverse events include sedation (histamine H1 antagonism), orthostatic hypotension (alpha-1 antagonism), and prolactin elevation (dopamine D2 antagonism). The metabolic liability is the most clinically significant disadvantage relative to xanomeline-trospium [26, 27].

Overall validation: High. Olanzapine has extensive clinical evidence, decades of postmarketing safety data, and broad regulatory approval across multiple indications.

Comparison to xanomeline-trospium: Xanomeline-trospium and olanzapine produce broadly comparable antipsychotic effect sizes. The critical differentiation is the adverse-event profile: xanomeline-trospium does not produce the metabolic syndrome, prolactin elevation, or neuromotor adverse events that are the principal clinical liabilities of olanzapine. Olanzapine has the advantage of extensive long-term data, multiple approved indications, and low cost as a generic product.

12.2 Aripiprazole

Mechanism: Atypical antipsychotic; partial agonist at dopamine D2 and serotonin 5-HT1A receptors; antagonist at serotonin 5-HT2A receptors [28].

Development trajectory: Developed by Otsuka; FDA-approved in 2002 for schizophrenia, subsequently approved for bipolar disorder, major depressive disorder (adjunctive), irritability associated with autism, and Tourette's disorder. The long-acting injectable formulation (Aristada, Abilify Maintena) extended the clinical application.

Novelty: Moderate. Aripiprazole introduced the concept of dopamine D2 partial agonism (the "dopamine system stabilizer" hypothesis), which was mechanistically novel at the time of its introduction. However, the compound still operates within the dopamine receptor pharmacology paradigm.

Effect size: Aripiprazole effect sizes on PANSS total score in pivotal trials are in the range of Cohen's d 0.3 to 0.5, somewhat lower than xanomeline-trospium in the EMERGENT trials but within the range observed across antipsychotic agents [28].

Promising potential: Low for innovation; high for current clinical utility. Aripiprazole is a mature product with multiple formulations, extensive generic competition, and broad indications.

Side-effect profile: Aripiprazole has a more favorable metabolic profile than olanzapine, with less weight gain and lower risk of metabolic syndrome. However, it can produce akathisia (10 to 15 percent), insomnia, restlessness, and extrapyramidal symptoms at higher doses. Prolactin elevation is minimal. The akathisia profile is a clinically significant disadvantage in some patients [28].

Overall validation: High. Extensive clinical evidence base across multiple indications and formulations.

Comparison to xanomeline-trospium: Xanomeline-trospium offers a fundamentally different mechanism that avoids the neuromotor adverse events (akathisia, extrapyramidal symptoms) that are the principal liabilities of aripiprazole. Aripiprazole has the advantage of a broader indication portfolio, multiple formulations (including long-acting injectables), and extensive long-term safety data.

12.3 Emraclidine (CVL-231)

Mechanism: Selective M4 muscarinic acetylcholine receptor positive allosteric modulator (PAM). Unlike xanomeline, which binds the orthosteric (acetylcholine-binding) site, emraclidine binds a topographically distinct allosteric site on the M4 receptor and enhances the response to endogenous acetylcholine without directly activating the receptor in the absence of agonist [29].

Development trajectory: Developed by Cerevel Therapeutics (acquired by AbbVie in 2024). A Phase 1b trial in schizophrenia reported safety and preliminary efficacy signals. The Phase 2 EMPOWER trial (NCT05227703) in patients with schizophrenia evaluated two doses of emraclidine versus placebo over 6 weeks. In December 2023, AbbVie reported that the EMPOWER trial did not meet its primary endpoint (change from baseline in PANSS total score) at either dose [29].

Novelty: High. The M4 PAM mechanism is distinct from the orthosteric agonism of xanomeline. Allosteric modulation preserves the spatiotemporal pattern of endogenous cholinergic signaling and avoids the desensitization or overstimulation that can occur with orthosteric agonism. This is the most mechanistically novel of the muscarinic-targeted comparators.

Effect size: The Phase 2 trial did not demonstrate a statistically significant effect on the primary endpoint. The negative Phase 2 readout limits confidence in the effect size.

Promising potential: Moderate. The Phase 2 failure has reduced enthusiasm, but the mechanistic novelty of M4 PAM remains of interest for further development. AbbVie has indicated continued investigation of the mechanism.

Side-effect profile: Emraclidine was generally well tolerated in Phase 1b and Phase 2 studies, with no dose-limiting cholinergic adverse events reported. The absence of gastrointestinal adverse events is consistent with the allosteric mechanism, which does not activate muscarinic receptors in the gastrointestinal tract in the absence of endogenous acetylcholine.

Overall validation: Low. The negative Phase 2 readout is the principal limitation. The compound has not demonstrated clinical efficacy in a randomized controlled trial.

Comparison to xanomeline-trospium: Emraclidine represents a more selective and theoretically cleaner approach to muscarinic M4 pharmacology. However, it has failed to demonstrate clinical efficacy in its Phase 2 trial, while xanomeline-trospium has demonstrated consistent efficacy across three positive Phase 3 trials and has received FDA approval. Xanomeline-trospium has the advantage of proven efficacy, regulatory approval, and the additional M1-mediated procognitive mechanism. Emraclidine has the theoretical advantage of selectivity and the absence of gastrointestinal adverse events.

12.4 Cariprazine

Mechanism: Atypical antipsychotic; partial agonist at dopamine D2 and D3 receptors, with preferential affinity for the D3 receptor. The D3-preferring profile distinguishes cariprazine from aripiprazole and brexpiprazole [30].

Development trajectory: Developed by Gedeon Richter and Allergan (now AbbVie); FDA-approved in 2015 for schizophrenia and in 2019 for bipolar depression. Studied specifically for negative symptoms of schizophrenia in the RGH-188-005 trial, which demonstrated superiority over risperidone on the PANSS negative symptom factor score.

Novelty: Moderate. The D3-preferring partial agonist mechanism represents an incremental advance within the dopamine receptor pharmacology paradigm but does not represent a mechanistic class break.

Effect size: Cariprazine effect sizes on PANSS total score are in the range of Cohen's d 0.3 to 0.5 in acute schizophrenia trials. The compound has demonstrated a specific effect on negative symptoms (the RGH-188-005 trial against risperidone), an area where most antipsychotics show only modest secondary effects [30].

Promising potential: Moderate. Active clinical use with a differentiated profile for negative symptoms. Generic competition is approaching.

Side-effect profile: Cariprazine produces akathisia (approximately 10 percent), insomnia, and extrapyramidal symptoms. Weight gain is modest (approximately 1 to 2 kg). Prolactin elevation is minimal. The long half-life (2 to 4 days for the parent compound, 1 to 3 weeks for the active metabolite DDCAR) produces a delayed onset and offset of both effects and side effects.

Overall validation: Moderate to high. Approved for two indications with a specific differentiation on negative symptoms.

Comparison to xanomeline-trospium: Xanomeline-trospium offers a completely different mechanism and avoids all neuromotor adverse events. Cariprazine has a specific negative-symptom differentiation that may be clinically relevant for patients with predominant negative symptoms, though xanomeline-trospium also demonstrated significant effects on PANSS negative subscales in the EMERGENT pooled analysis (effect size 0.35).

12.5 Pimavanserin

Mechanism: Selective serotonin 5-HT_{2A} receptor inverse agonist/antagonist. Does not bind dopamine D₂ receptors. The only other non-D₂-blocking antipsychotic mechanism besides xanomeline-trospium to receive FDA approval for a psychosis-related indication [31].

Development trajectory: Developed by Acadia Pharmaceuticals; FDA-approved in 2016 for hallucinations and delusions associated with Parkinson's disease psychosis. Not approved for schizophrenia. The HARMONY study evaluated pima-

vanserin for dementia-related psychosis across multiple dementia subtypes; an sNDA for this broader indication was submitted to the FDA and received a Complete Response Letter in 2022.

Novelty: High. Pimavanserin, like xanomeline-trospium, introduced a non-D2-blocking antipsychotic mechanism. However, the 5-HT_{2A} inverse agonist mechanism is distinct from the muscarinic agonist mechanism, targeting serotonergic rather than cholinergic neurotransmission.

Effect size: In the pivotal Parkinson's disease psychosis trial, pimavanserin produced a modest effect on the SAPS-PD (Scale for the Assessment of Positive Symptoms adapted for Parkinson's disease), with a treatment difference of approximately 3.1 points versus placebo. Effect sizes are generally smaller than those observed with xanomeline-trospium in schizophrenia trials, though the indication and population differ [31].

Promising potential: Moderate. Approved for one indication; the broader dementia-related psychosis indication has not been approved. The compound remains the only approved treatment for Parkinson's disease psychosis that does not exacerbate motor symptoms.

Side-effect profile: Generally well tolerated. The principal adverse events are peripheral edema, nausea, and confusion. QT prolongation has been observed, and the prescribing label includes a warning regarding this risk. No extrapyramidal symptoms, weight gain, or prolactin elevation.

Overall validation: Moderate. Approved for a single indication with a specific clinical niche (Parkinson's disease psychosis). The broader psychosis indication has not been established.

Comparison to xanomeline-trospium: Both compounds represent mechanistically novel, non-D2-blocking approaches to psychosis. Xanomeline-trospium has demonstrated larger effect sizes in a broader patient population (schizophrenia versus Parkinson's disease psychosis) and has achieved FDA approval for schizophrenia, a larger and more clinically significant indication. Pimavanserin has the advantage of established use in Parkinson's disease psychosis, where dopamine D₂ antagonists are contraindicated.

12.6 Comparator summary

Among the five comparators, **olanzapine** and **aripiprazole** represent the established standard of care for schizophrenia, with extensive clinical evidence but significant adverse-event liabilities (metabolic syndrome for olanzapine, akathisia for aripiprazole) that xanomeline-trospium avoids. **Emraclidine** represents the most mechanistically related comparator (muscarinic M4 modulation) but has failed in Phase 2 and lacks clinical validation. **Cariprazine** offers incremental innovation within the dopamine pharmacology paradigm with a specific negative-symptom claim. **Pimavanserin** is the closest mechanistic parallel as a non-D2-blocking antipsychotic but serves a different and narrower patient population.

Xanomeline-trospium occupies a unique position as the first and only muscarinic agonist-based treatment approved for schizophrenia, the first non-D2-blocking antipsychotic approved for this indication, and the only antipsychotic that produces no metabolic syndrome, no prolactin elevation, no extrapyramidal symptoms, and no tardive dyskinesia in its clinical trial program. The effect size on PANSS total score (Cohen's d 0.65 pooled) is comparable to the most efficacious established antipsychotics. The principal limitation is the gastrointestinal adverse-event profile (nausea, vomiting, dyspepsia), which, though generally transient and manageable, represents a tolerability consideration. The long-term safety database (52 weeks in 566 patients) is smaller than those available for the established comparators, and postmarketing surveillance will be necessary to characterize rare adverse events that may not have been captured in the registration program. The ongoing Alzheimer's disease pipeline (ADEPT, ADAGIO, cognitive impairment trials) represents a substantial expansion of the therapeutic reach of the muscarinic agonist mechanism beyond schizophrenia.

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