

RESEARCH MONOGRAPH . COMPOUND PROFILE

CDD-0102

A functionally selective partial agonist at the M1 muscarinic acetylcholine receptor developed at the University of Toledo as a cognitive enhancer and neuroprotective agent for Alzheimer's disease, distinguished from earlier muscarinic agonists by subtype selectivity, low cholinergic adverse-event burden, and oral bioavailability.

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ABSTRACT

CDD-0102, the hydrochloride salt of 5-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,4,5,6-tetrahydropyrimidine (designated CDD-0102A in its salt form), is a functionally selective partial agonist at the M1 subtype of the muscarinic acetylcholine receptor developed at the University of Toledo College of Pharmacy under the direction of W.S. Messer Jr. as a candidate therapeutic for Alzheimer's disease and related cognitive disorders. The compound occupies the orthosteric acetylcholine-binding site of the M1 receptor with partial agonist intrinsic activity sufficient to activate phospholipase C-coupled signaling, stimulate non-amyloidogenic processing of amyloid precursor protein (APP) through alpha-secretase, and enhance cognitive function in rodent models of cholinergic deficit, while exhibiting minimal functional activity at M2, M4, and M5 muscarinic subtypes and only weak activity at M3 receptors. This functional selectivity profile distinguishes CDD-0102 from the first-generation M1-preferring muscarinic agonists (xanomeline, sabcomeline, talsaclidine, cevimeline) that produced dose-limiting cholinergic adverse events (salivation, gastrointestinal disturbance, diaphoresis) attributable to activation of peripheral M2 and M3 receptors, a limitation that terminated or constrained the clinical development of each of those compounds in the Alzheimer's indication. The pharmacological characterization of CDD-0102 encompasses M1-selective receptor binding, stimulation of soluble APP-alpha (sAPPalpha) secretion from Chinese hamster ovary cells stably expressing human M1 receptors, neuroprotective activity in cell culture, brain penetration following systemic administration in rodents, oral bioavailability, and a favorable acute toxicity profile.

In behavioral pharmacology, CDD-0102A administered intraperitoneally at doses of 0.03 to 1.0 mg/kg enhances delayed spontaneous alternation in a four-arm cross maze (a measure of spatial working memory) and facilitates strategy switching between place and visual-cue discriminations (a measure of cognitive flexibility), with both effects following a dose-dependent profile and occurring at doses below the threshold for salivation (approximately 0.3 mg/kg intraperitoneal for the minimum effective salivation dose, with an estimated ED₅₀ for salivation of 2.0 mg/kg). More recent preclinical work has extended the pharmacological profile to autism spectrum disorder models, demonstrating that CDD-0102A attenuates stereotyped motor behaviors (self-grooming, digging) and modulates glutamate efflux in dorsolateral striatum of the BTBR T+ Itpr3tf/J mouse, a model of autism-relevant repetitive behavior and social deficit. The compound advanced through preclinical development with support from the National Center for Advancing Translational Sciences (NCATS) Bridging Interventional Development Gaps (BrIDGs) program, which funded the IND-enabling studies including synthetic scale-up, formulation, pharmacokinetics, and toxicology. An Investigational New Drug (IND) application was filed with the United States Food and Drug Administration, and Phase 1 clinical testing was initiated. Published results from Phase 1 clinical evaluation have not appeared in the peer-reviewed literature as of the most recent monograph revision. The compound is not registered as a marketed medicine in any jurisdiction. This monograph reviews the chemistry, synthesis, and structural class of CDD-0102; the M1 muscarinic receptor pharmacology in molecular and functional detail; the preclinical evidence base across Alzheimer's disease, cognitive flexibility, and autism-relevant endpoints; the available pharmacokinetic

characterization; sourcing and quality verification considerations for research applications; reconstitution and handling; stack-interaction considerations; the adverse-event and safety profile; and a comparative assessment of five M1 muscarinic receptor agonist candidates (xanomeline, sabcomeline, talsaclidine, AF267B, cevimeline) against CDD-0102 on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Preferred compound designation: CDD-0102.

Salt form designation: CDD-0102A (the hydrochloride salt, the form used in all published pharmacological and behavioral studies).

Development codes: CDD-0102 (University of Toledo, College of Pharmacy, Department of Medicinal and Biological Chemistry). The development code is the canonical identifier across all published literature from the Messer laboratory and the NCATS BrIDGs program [1, 2].

Chemical Abstracts Service registry number: 1196130-86-5 (hydrochloride salt). The free base CAS number is not separately registered in the common chemical supplier databases; the hydrochloride is the standard research and development form.

DrugBank identifier: DB16945.

International Union of Pure and Applied Chemistry name: 5-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,4,5,6-tetrahydropyrimidine hydrochloride (salt form). The free base IUPAC name is 5-(3-ethyl-1,2,4-oxadiazol-5-yl)-1,4,5,6-tetrahydropyrimidine.

1.2 Structural class and chemistry

CDD-0102 belongs to the tetrahydropyrimidine-oxadiazole structural class, a series of compounds developed at the University of Toledo through systematic medicinal chemistry optimization of tetrahydropyrimidine derivatives as selective muscarinic receptor agonists [3, 4]. The structural class was designed to incorporate the 1,4,5,6-tetrahydropyrimidine ring (which provides the cationic amidinium pharmacophore required for muscarinic receptor recognition) linked through the 5-position to a 1,2,4-oxadiazole heterocycle bearing an ethyl substituent at the 3-position. The oxadiazole ring was identified through structure-activity exploration as conferring improved M1 selectivity relative to earlier tetrahydropyrimidine derivatives bearing ester, thioester, or alkynyl substituents at the same position [3, 4].

Molecular formula: C₈H₁₂N₄O (free base); C₈H₁₃ClN₄O (hydrochloride salt).

Exact mass: 180.1011 g/mol (free base, monoisotopic).

Molecular weight: 180.21 g/mol (free base); 216.67 g/mol (hydrochloride salt).

SMILES notation: CCC1=NOC(=N1)C1CNC=NC1 (free base).

Physical properties: White to off-white crystalline powder as the hydrochloride salt. Soluble in water and in dimethyl sulfoxide; soluble in methanol and ethanol. The hydrochloride salt is the standard form for aqueous formulation and for in vivo administration.

Stereochemistry: CDD-0102 contains one stereocenter at the 5-position of the tetrahydropyrimidine ring. The published literature from the Messer laboratory reports the compound as the racemic mixture; the individual enantiomers have not been separately characterized in published pharmacological studies. Investigators should note that the stereochemistry may influence receptor binding affinity and functional selectivity, as has been demonstrated for other tetrahydropyrimidine muscarinic agonists.

1.3 Synthesis

The synthesis of CDD-0102 proceeds through a convergent strategy involving separate preparation of the 1,2,4-oxadiazole ring system and the tetrahydropyrimidine ring, followed by their coupling. The published synthetic routes from the Messer laboratory describe the preparation of 3-ethyl-1,2,4-oxadiazole-5-carboxaldehyde derivatives and their condensation with 1,3-diaminopropane equivalents to form the tetrahydropyrimidine ring, or alternatively the direct functionalization of a pre-formed tetrahydropyrimidine at the 5-position with an activated oxadiazole electrophile [3, 4, 5]. The hydrochloride salt is prepared by treatment of the free base with hydrogen chloride in an appropriate solvent (diethyl ether or dioxane) followed by recrystallization.

Industrial scale-up synthesis was performed under the NCATS BrIDGs program to produce quantities sufficient for IND-enabling toxicology studies and Phase 1 clinical material [2]. The scale-up route and process chemistry details have not been published in the open literature. Research-grade synthetic procedures are accessible through the University of Toledo patent filings and through the published medicinal chemistry literature from the Messer laboratory [5, 6].

Molecular modeling studies have identified key interactions between the tetrahydropyrimidine-oxadiazole scaffold and the M1 muscarinic receptor binding site, including hydrogen bonding between the oxadiazole moiety and Thr192 and additional interactions with Asn382 in the receptor orthosteric pocket [3]. These modeling studies guided the selection of the ethyl substituent at the 3-position of the oxadiazole as the optimal balance between M1 affinity and subtype selectivity.

2. Abstract

CDD-0102 (CDD-0102A as the hydrochloride salt) is a functionally selective partial agonist at the M1 subtype of the muscarinic acetylcholine receptor (mAChR), developed at the University of Toledo by W.S. Messer Jr. and colleagues as a candidate therapeutic for cognitive impairment associated with Alzheimer's disease [1, 2]. The compound was designed through iterative medicinal chemistry optimization of tetrahydropyrimidine scaffolds to achieve selective activation of M1-coupled signaling pathways (phospholipase C, protein kinase C, mitogen-activated protein kinase) while minimizing functional activity at M2, M3, M4, and M5 muscarinic receptor subtypes [3, 4].

The rationale for M1-selective muscarinic agonism in Alzheimer's disease rests on three convergent observations. First, the M1 receptor is the predominant muscarinic subtype in cortex and hippocampus, the brain regions most affected by cholinergic degeneration in Alzheimer's disease, and M1 receptor density is relatively preserved in early and moderate disease even as presynaptic cholinergic markers (choline acetyltransferase activity, vesicular acetylcholine transporter expression) decline [7, 8]. Second, activation of M1 receptors stimulates the non-amyloidogenic alpha-secretase processing of amyloid precursor protein (APP), increasing the release of the neurotrophic soluble fragment sAPPalpha and decreasing the production of the amyloidogenic Abeta peptide [9, 10]. Third, M1 receptor activation enhances cholinergic neurotransmission in cortical and hippocampal circuits through postsynaptic excitatory effects, supporting cognitive processes (working memory, attention, cognitive flexibility) that are impaired in Alzheimer's disease and related conditions [7].

CDD-0102 demonstrated efficacy in preclinical models of cognitive impairment. In rats with excitotoxic lesions of the nucleus basalis magnocellularis (the principal basal forebrain cholinergic nucleus projecting to cortex), CDD-0102 improved memory function at doses that did not produce cholinergic adverse effects [1]. In intact mice, CDD-0102A at 0.1 to 1.0 mg/kg intraperitoneally enhanced delayed spontaneous alternation performance (spatial working memory) and at 0.03 to 0.1 mg/kg facilitated strategy switching between place and visual-cue discriminations (cognitive flexibility), with both cognitive effects occurring at doses below the sali-

vation threshold [11]. In the BTBR T+ Itpr3tf/J mouse model of autism, CDD-0102A at 1.2 mg/kg attenuated stereotyped motor behaviors and modulated glutamate efflux in dorsolateral striatum [12, 13].

The compound advanced through IND-enabling preclinical development with support from the NCATS BrIDGs program and successfully achieved IND filing with the FDA [2]. Phase 1 clinical testing was initiated. Published clinical results have not appeared as of the most recent monograph revision. The compound is not registered as a marketed medicine.

This monograph documents chemistry, synthesis, M1 muscarinic receptor pharmacology, the preclinical evidence base, available pharmacokinetic data, sourcing and quality verification, reconstitution and handling, stack-interaction considerations, adverse-event profile, and a structured comparative assessment of five M1 muscarinic receptor agonist candidates (xanomeline, sabcomeline, talsaclidine, AF267B, cevimeline) against CDD-0102 on five standards: novelty, effect size, promising potential, side-effect profile, and overall validation.

3. Discovery and Development History

3.1 Origin

CDD-0102 was synthesized at the Department of Medicinal and Biological Chemistry, College of Pharmacy, University of Toledo (Toledo, Ohio) as part of a systematic medicinal chemistry program directed by W.S. Messer Jr. to develop selective muscarinic agonists for the treatment of Alzheimer's disease. The program began in the early 1990s with the characterization of tetrahydropyrimidine derivatives as functional muscarinic agonists and the identification of structural features that confer selectivity for the M1 subtype [3, 4, 14].

The design rationale was grounded in the cholinergic hypothesis of Alzheimer's disease, which posits that degeneration of basal forebrain cholinergic neurons (the nucleus basalis of Meynert, the medial septal nucleus, and the diagonal band nuclei) produces cortical and hippocampal cholinergic deficit that is a principal substrate for the cognitive impairment characteristic of the disease [7, 8]. The acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) address this deficit indirectly by prolonging the action of remaining endogenous acetylcholine. Direct muscarinic agonists were pursued as an alternative strategy that would not depend on residual presynaptic cholinergic function and that could additionally recruit M1-mediated neuroprotective and anti-amyloidogenic signaling cascades [9].

3.2 Early tetrahydropyrimidine series

The Messer laboratory characterized a series of 1,4,5,6-tetrahydropyrimidine derivatives bearing various 5-position substituents (esters, thioesters, alkynyl groups, and heterocyclic groups) for functional activity at M1, M2, M3, M4, and M5 muscarinic receptor subtypes expressed in Chinese hamster ovary (CHO) cells [3, 4, 14]. The tetrahydropyrimidine ring system was selected as the core pharmacophore because the amidinium cation mimics the quaternary ammonium of acetylcholine and provides high-affinity recognition at the orthosteric binding site of muscarinic receptors. Structure-activity studies identified that the nature of the 5-position substituent was the principal determinant of subtype selectivity and of functional efficacy (full agonist versus partial agonist versus antagonist activity at each subtype).

The 1,2,4-oxadiazole series, of which CDD-0102 is the lead compound, was identified as conferring a particularly favorable selectivity profile: partial agonist activity at M1, weak partial agonist activity at M3, and minimal or no activity at M2, M4, and M5 [1, 3]. The ethyl substituent at the 3-position of the oxadiazole was selected on the basis of optimal M1 affinity and selectivity from a subseries varying the alkyl chain length.

3.3 Preclinical characterization

The Messer 2002 Drug Development Research report, "Development of CDD-0102 as a selective M1 agonist for the treatment of Alzheimer's disease," presented the initial comprehensive preclinical profile of the compound [1]. Key findings included: stimulation of sAPP α secretion from CHO-K1 cells expressing human M1 receptors; brain penetration following intraperitoneal administration in rats (assessed by direct tissue concentration measurement); improvement of memory function in rats with ibotenic acid lesions of the nucleus basalis magnocellularis; oral bioavailability in rodents; a low acute toxicity profile; and a favorable side-effect profile relative to xanomeline and other first-generation muscarinic agonists.

A poster presentation at the Alzheimer's Association International Conference (Messer et al., 2005) extended the preclinical evaluation to include additional cognitive endpoints and toxicology assessments, confirming the safety margin between cognitive-enhancing and adverse-effect doses [15].

3.4 NCATS BrIDGs program and IND filing

The National Center for Advancing Translational Sciences (NCATS) selected CDD-0102 for its Bridging Interventional Development Gaps (BrIDGs) program, which provides federal resources for IND-enabling studies for academic-origin therapeutic candidates that address unmet medical needs [2]. The BrIDGs support funded synthetic scale-up chemistry, Good Manufacturing Practice (GMP) manufacturing of clinical-grade material, formulation development, formal pharmacokinetics and toxicology studies in two species, and preparation of the IND application. The project was led by W.S. Messer Jr. at the University of Toledo.

The NCATS BrIDGs project page reports that the investigator successfully filed an IND application using BrIDGs-generated data and initiated Phase 1 clinical testing [2]. The specific timeline, clinical sites, dosing regimens, and results of the Phase 1

study have not been published in the peer-reviewed literature as of the most recent monograph revision.

3.5 Extension to autism spectrum disorder

Beginning approximately 2019, the Blakely and Messer laboratories extended the pharmacological characterization of CDD-0102A to the BTBR T+ Itpr3tf/J (BTBR) mouse, an inbred strain that exhibits autism-relevant phenotypes including elevated repetitive motor behaviors (self-grooming, digging), social interaction deficits, and reversal learning impairments [12, 13]. This work represents the most recent published preclinical expansion of the CDD-0102 pharmacology beyond the original Alzheimer's disease indication.

4. Mechanism of Action

CDD-0102 is a functionally selective partial agonist at the M1 muscarinic acetylcholine receptor. Its principal molecular activity, characterized in heterologous expression systems and confirmed in native tissue and behavioral models, is selective activation of M1-coupled intracellular signaling cascades at the orthosteric (acetylcholine-binding) site of the receptor.

4.1 Muscarinic receptor classification and M1 receptor biology

The muscarinic acetylcholine receptors are a family of five G-protein-coupled receptors (M1 through M5) that mediate the metabotropic actions of acetylcholine in the central and peripheral nervous systems. The M1, M3, and M5 subtypes couple primarily to Gq/11 heterotrimeric G proteins, activating phospholipase C (PLC) to produce inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG), with consequent intracellular calcium mobilization and protein kinase C (PKC) activation. The M2 and M4 subtypes couple primarily to Gi/o G proteins, inhibiting adenylyl cyclase and modulating potassium and calcium channels [7, 16].

The M1 receptor is the predominant muscarinic subtype in cerebral cortex, hippocampus, and striatum, where it is expressed primarily on postsynaptic neurons. In cortex and hippocampus, M1 activation enhances neuronal excitability, facilitates long-term potentiation (a cellular correlate of learning and memory), and modulates the processing of amyloid precursor protein toward the non-amyloidogenic alpha-secretase pathway [7, 8, 9]. In Alzheimer's disease, M1 receptor density is relatively preserved in early and moderate stages despite the degeneration of presynaptic cholinergic afferents from the basal forebrain, making the M1 receptor an attractive direct therapeutic target that does not depend on residual cholinergic innervation [8].

4.2 M1-selective partial agonism

CDD-0102 binds the orthosteric site of the M1 muscarinic receptor and activates PLC-coupled signaling with partial agonist efficacy. The partial agonist character means that CDD-0102 produces submaximal activation of M1-coupled signaling relative to the full agonist acetylcholine (or the full synthetic agonist carbachol). This partial agonism has two pharmacologically important consequences [1, 11].

First, a partial agonist requires only low fractional receptor occupancy to produce its maximal effect, and the relationship between occupancy and effect is compressed relative to a full agonist. This means that efficacious cognitive enhancement can be achieved at receptor occupancies below those that would recruit the full spectrum of M1-coupled effectors, potentially conferring a more targeted pharmacological profile.

Second, a partial agonist has the capacity to function as a buffer of cholinergic tone: under conditions of low endogenous acetylcholine (as in the cholinergic-depleted Alzheimer brain), the partial agonist provides a basal level of M1 activation; under conditions of high endogenous acetylcholine (as during phasic cholinergic transmission associated with attention and reward), the partial agonist competes with acetylcholine for the receptor and limits maximal activation. This buffering property has been advanced by Messer and colleagues as a pharmacological advantage for chronic dosing in neurodegenerative conditions where cholinergic tone is variable and progressively declining [1, 11].

4.3 Subtype selectivity

The functional selectivity of CDD-0102 was characterized in CHO cells stably expressing individual human muscarinic receptor subtypes (hM1 through hM5). The compound displays partial agonist activity at M1, weak partial agonist activity at M3 (substantially lower intrinsic activity than at M1), and minimal or no functional activity at M2, M4, and M5 subtypes at concentrations producing full M1 activation [1, 3, 4].

The M1 selectivity is functionally defined rather than binding-affinity defined. The tetrahydropyrimidine-oxadiazole scaffold binds to the highly conserved orthosteric site of all muscarinic subtypes with relatively similar affinity, but produces differential activation of the G-protein-coupled signaling cascades at each subtype. This pattern, termed "functional selectivity" or "biased agonism" in the re-

ceptor pharmacology literature, arises from subtype-specific receptor-G-protein coupling efficiencies and from differential stabilization of active versus inactive receptor conformations by the partial agonist ligand [3, 17].

The practical consequence is that CDD-0102 activates M1-mediated cortical and hippocampal signaling at doses that do not produce the peripheral M2-mediated bradycardia, M3-mediated salivation and gastrointestinal hypermotility, or M2/M3-mediated diaphoresis that limited the clinical development of xanomeline, sabcomeline, and talsaclidine [1, 18].

4.4 APP processing and neuroprotection

Activation of M1 muscarinic receptors stimulates the alpha-secretase cleavage of amyloid precursor protein (APP), producing the soluble neurotrophic ectodomain fragment sAPPalpha and correspondingly reducing the amyloidogenic beta-secretase cleavage that generates Abeta peptides [9, 10]. CDD-0102 stimulated sAPPalpha secretion from CHO-K1 cells stably expressing human M1 receptors in a concentration-dependent manner [1]. The signaling pathway connecting M1 activation to alpha-secretase involves PKC-dependent and mitogen-activated protein kinase (MAPK/ERK)-dependent routes, both of which converge on the activation of ADAM10 and ADAM17 (TACE), the principal constitutive and regulated alpha-secretases [9, 10].

CDD-0102 also exhibited neuroprotective activity in cell culture models, consistent with the known neuroprotective effects of M1 muscarinic activation through Akt/PKB signaling, Bcl-2 family modulation, and the neurotrophic actions of sAPPalpha [1]. The specific cell culture models and the magnitude of neuroprotection have not been detailed in full in the published literature.

4.5 Glutamate modulation in striatal circuits

The extension of CDD-0102A pharmacology to the BTBR autism model revealed a previously uncharacterized activity: modulation of glutamate efflux in dorsolateral striatum [13]. In BTBR mice, which exhibit elevated and dysregulated glutamate signaling in dorsomedial and dorsolateral striatum relative to C57BL/6J (B6) controls, CDD-0102A at 1.2 mg/kg attenuated the magnitude of bidirectional changes in glutamate efflux from dorsolateral striatum (but not dorsomedial striatum) during the expression of stereotyped motor behaviors [13]. The mechanism plausibly involves

M1-mediated modulation of corticostriatal glutamatergic projection neurons or of striatal cholinergic interneurons that regulate local glutamate release. This activity extends the potential therapeutic applications of CDD-0102 beyond the Alzheimer's disease cholinergic deficit framework to a broader set of conditions involving striatal circuit dysfunction.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption and oral bioavailability

CDD-0102 exhibits oral bioavailability in rodents, a property that was a principal selection criterion for advancement to IND-enabling development [1, 2]. The specific oral bioavailability value (expressed as a percentage of intravenous or intraperitoneal exposure) has not been published in the peer-reviewed literature. The NCATS BrIDGs program conducted formal pharmacokinetic studies in two species (rodent and non-rodent) as part of the IND-enabling package; these data were included in the IND application but have not been published [2].

The compound is absorbed from the gastrointestinal tract following oral administration. The tetrahydropyrimidine-oxadiazole scaffold is a small, moderately polar molecule (molecular weight 180.21 for the free base) with physicochemical properties (calculated LogP approximately 0.5 to 1.0, polar surface area approximately 65 to 70 square angstroms, fewer than 5 hydrogen bond donors and acceptors) consistent with favorable oral absorption by passive transcellular permeation.

5.2 Distribution and brain penetration

CDD-0102 penetrates the blood-brain barrier following systemic administration. Brain penetration was demonstrated by direct measurement of compound concentrations in brain tissue following intraperitoneal administration in rats [1]. The compound achieved brain concentrations sufficient to activate M1 receptors, as evidenced by the cognitive-enhancing behavioral effects at systemic doses consistent with central receptor engagement.

The volume of distribution, plasma protein binding, and tissue partitioning coefficients have not been published. The small molecular size, moderate lipophilicity, and favorable polar surface area of the compound predict moderate to good central nervous system penetration, consistent with the observed behavioral pharmacology.

5.3 Metabolism

The metabolic pathways of CDD-0102 have not been detailed in the published literature. The 1,2,4-oxadiazole ring is metabolically stable in most species; the tetrahydropyrimidine ring is susceptible to oxidative metabolism (ring hydroxylation, N-dealkylation) by hepatic cytochrome P450 enzymes. The ethyl substituent on the oxadiazole is susceptible to omega-hydroxylation and oxidation to the corresponding carboxylic acid. Formal metabolite identification studies were conducted as part of the NCATS BrIDGs IND-enabling program but have not been published [2].

5.4 Elimination

Elimination pathways have not been published. Based on the physicochemical properties and the metabolic susceptibility profile of the tetrahydropyrimidine-oxadiazole scaffold, elimination is predicted to be predominantly metabolic (hepatic biotransformation) rather than direct renal clearance of unchanged drug.

5.5 Routes of administration

Two principal routes have been used in published preclinical studies: intraperitoneal injection (the standard route in the behavioral pharmacology literature, at doses of 0.03 to 3.0 mg/kg in mice and rats) and oral administration (confirmed in the Messer 2002 report as bioavailable; specific oral doses and bioavailability parameters not published) [1, 11, 12, 13]. The NCATS BrIDGs Phase 1 clinical material was formulated for a route of administration consistent with clinical dosing (presumably oral), though the specific formulation has not been disclosed.

5.6 Special populations

No special-population pharmacokinetic data (pediatric, geriatric, hepatic impairment, renal impairment) have been published. The compound has not been studied in pregnancy or lactation.

6. Preclinical Pharmacology

6.1 Cognitive enhancement in cholinergic lesion models

The Messer 2002 report demonstrated that CDD-0102 improved memory function in rats with bilateral ibotenic acid lesions of the nucleus basalis magnocellularis, the principal basal forebrain cholinergic nucleus projecting to cortex [1]. The lesion model produces cortical cholinergic denervation that mimics the presynaptic cholinergic deficit of Alzheimer's disease. CDD-0102 at doses producing cognitive enhancement did not produce the cholinergic adverse effects (salivation, lacrimation, diarrhea, urination) that limited the utility of the comparator compound xanomeline in the same model [1].

6.2 Working memory and cognitive flexibility

The Ragozzino et al. (2012) report in the Journal of Pharmacology and Experimental Therapeutics provided the most detailed behavioral pharmacology characterization of CDD-0102A [11]. Key findings included:

Working memory: CDD-0102A administered intraperitoneally 30 minutes before testing at 0.1, 0.3, and 1.0 mg/kg significantly enhanced delayed spontaneous alternation performance in a four-arm cross maze in intact mice. The effect was dose-dependent, with the 0.3 and 1.0 mg/kg doses producing the largest enhancements. The delayed alternation task requires spatial working memory over a 30-second delay and is sensitive to cholinergic manipulation.

Cognitive flexibility: CDD-0102A at 0.03 and 0.1 mg/kg significantly enhanced strategy switching between a place discrimination and a visual-cue discrimination in mice. Analysis of error types revealed that CDD-0102A improved both the initial inhibition of the previously relevant strategy (perseverative errors) and the maintenance of the newly relevant strategy once selected (regressive errors) [11]. This dual effect on perseveration and maintenance is consistent with M1-mediated modulation of prefrontal cortical circuits that support cognitive flexibility.

Locomotor activity: CDD-0102A at cognitive-enhancing doses did not alter general locomotor activity, indicating that the cognitive effects are not secondary to changes in arousal, motivation, or motor function [11].

6.3 Salivation dose-response

Salivation is the cardinal peripheral cholinergic adverse effect of muscarinic agonists and was the principal dose-limiting toxicity for first-generation M1-preferring agonists in clinical trials. CDD-0102A produced salivation in mice at doses substantially higher than those required for cognitive enhancement. The minimum dose required to induce salivation was approximately 0.3 mg/kg intraperitoneal, and the estimated ED50 for salivation was 2.0 mg/kg [11]. By comparison, the cognitive-enhancing doses ranged from 0.03 to 1.0 mg/kg, providing a safety margin of approximately 2- to 67-fold between the minimum cognitive-enhancing dose and the salivation ED50. This safety margin compares favorably to xanomeline, for which salivation and other cholinergic adverse effects occur at or near the cognitive-enhancing dose range [18].

6.4 Autism-relevant behavioral pharmacology

Two reports from the Blakely and colleagues laboratory extended CDD-0102A pharmacology to the BTBR mouse model of autism:

Stereotyped motor behavior: Amodeo et al. (2022) reported in the *International Journal of Neuropsychopharmacology* that CDD-0102A at 1.2 mg/kg intraperitoneally significantly attenuated elevated self-grooming behavior and digging behavior in BTBR mice without affecting overall locomotor activity [12]. The 0.3 mg/kg dose did not significantly affect stereotyped behaviors. The effect was selective: CDD-0102A did not alter the already-low grooming and digging in B6 control mice, indicating that the compound attenuates pathologically elevated repetitive behavior rather than producing generalized behavioral suppression.

Reversal learning: In the same study, CDD-0102A at 1.2 mg/kg did not significantly improve reversal learning in BTBR mice in the specific task employed (a discrimination reversal in a T-maze), though a non-significant trend toward improvement was observed [12].

Glutamate efflux modulation: Amodeo et al. (2023) reported in ACS Chemical Neuroscience that CDD-0102A at 1.2 mg/kg differentially modulated glutamate efflux in striatal subregions of BTBR mice during the expression of stereotyped motor behaviors [13]. BTBR mice displayed significantly greater magnitude changes in glutamate efflux (both increases and decreases) from dorsomedial and dorsolateral striatum compared to B6 controls. CDD-0102A significantly dampened the magnitude of bidirectional glutamate changes in dorsolateral striatum but not dorsomedial striatum, and this glutamate modulation correlated with the attenuation of grooming behavior. The findings suggest that M1 muscarinic receptor activation in dorsolateral striatal circuits contributes to the regulation of repetitive motor behaviors and that homeostatic glutamate mechanisms are compromised in the BTBR model.

6.5 APP processing in vitro

CDD-0102 stimulated the secretion of sAPP α from CHO-K1 cells stably expressing human M1 muscarinic receptors in a concentration-dependent manner, consistent with M1-mediated activation of the α -secretase pathway [1]. The effect provides a molecular basis for the anti-amyloidogenic potential of the compound, complementing the cognitive-enhancing behavioral pharmacology with a disease-modifying mechanistic hypothesis relevant to Alzheimer's disease pathophysiology.

6.6 Neuroprotection

CDD-0102 displayed neuroprotective effects in cell culture models, consistent with M1-mediated activation of pro-survival signaling cascades (Akt/PKB, Bcl-2) and with the neurotrophic properties of sAPP α [1]. The specific cell types, challenge conditions (oxidative stress, excitotoxicity, amyloid-beta toxicity), and magnitudes of neuroprotection have not been detailed in published form.

7. Clinical Evidence Base

7.1 IND filing and Phase 1 initiation

The NCATS BrIDGs program page reports that the investigator (W.S. Messer Jr., University of Toledo) successfully filed an Investigational New Drug (IND) application with the United States Food and Drug Administration using data generated through the BrIDGs program and initiated Phase 1 clinical testing [2]. The IND-enabling package included synthetic scale-up chemistry, GMP manufacturing, formulation development, formal pharmacokinetics in two species, repeat-dose toxicology, genotoxicity testing, and safety pharmacology assessments.

7.2 Phase 1 clinical data

Published results from Phase 1 clinical evaluation of CDD-0102 have not appeared in the peer-reviewed literature or in publicly accessible conference proceedings as of the most recent monograph revision. The ClinicalTrials.gov registry does not contain a publicly listed study for CDD-0102 under that designation. The clinical status of the compound (whether Phase 1 is complete, whether Phase 2 planning is underway, or whether clinical development has been paused or discontinued) is not publicly documented.

7.3 Clinical context

CDD-0102 entered clinical development in the context of a historically difficult therapeutic area. No selective M1 muscarinic agonist has achieved regulatory approval for the treatment of Alzheimer's disease. The first-generation M1-preferring agonists (xanomeline, sabcomeline, talsaclidine, cevimeline) all produced dose-limiting cholinergic adverse effects attributable to insufficient subtype selectivity, and their clinical programs in Alzheimer's disease were discontinued or redirected [18, 19, 20]. The most clinically successful exploitation of the muscarinic agonist mechanism has been the combination of xanomeline with the peripherally restricted muscarinic antagonist trospium chloride (marketed as Cobenfy/KarXT), which was approved by the FDA in September 2024 for schizophrenia [21]. The xanomeline-tro-

spium approach addresses the peripheral adverse-effect limitation of xanomeline through pharmacological antagonism rather than through the receptor-level functional selectivity that CDD-0102 represents.

The CDD-0102 clinical program represents an alternative strategy: achieving tolerability through intrinsic M1 functional selectivity at the ligand-receptor level rather than through combination with a peripheral antagonist. Whether this strategy will produce adequate tolerability and efficacy in human patients remains to be determined by the clinical data.

8. Sourcing and Quality Verification

Research-grade CDD-0102A (the hydrochloride salt) is available from specialized chemical and pharmaceutical research suppliers. MedChemExpress lists the compound under catalog number HY-100748 at greater than 98 percent purity by HPLC [22]. Other specialty research chemical suppliers (BenchChem, ChemScene, and similar vendors) list the compound or can source it on request. Supply is in milligram quantities as the hydrochloride salt; gram-scale quantities may require custom synthesis.

The compound is not available as a pharmaceutical-grade registered medicine in any jurisdiction. All sourcing for research applications is research-grade material from chemical suppliers.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (181.11 for the protonated free base $[M+H]^+$, or 217.07 for the protonated hydrochloride form if analyzed as the salt)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation, with comparison to published spectral data from the Messer laboratory
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography for common synthesis solvents

Third-party analytical laboratories can provide independent verification of vendor certificates of analysis. The research-grade CDD-0102A market is small and niche; lot-to-lot variability may be more pronounced than for widely sourced research compounds, and on-receipt analytical confirmation is strongly recommended.

9. Reconstitution and Handling

CDD-0102A hydrochloride is soluble in water at room temperature. For in vivo research applications, the compound is typically dissolved in sterile normal saline (0.9 percent sodium chloride) or in phosphate-buffered saline at concentrations appropriate to the intended dose and injection volume. The published behavioral pharmacology studies used intraperitoneal injection in mice and rats at concentrations producing injection volumes of approximately 10 mL/kg body weight [11, 12, 13].

For in vitro applications, stock solutions can be prepared in dimethyl sulfoxide (DMSO) at concentrations of 10 to 100 mM and diluted into aqueous assay medium immediately before use. The final DMSO concentration in the assay should not exceed 0.1 percent (v/v) to avoid solvent effects on muscarinic receptor pharmacology.

Storage of the solid compound at -20 degrees Celsius under desiccation is recommended for long-term stability. Aqueous stock solutions should be prepared fresh for each experimental session or aliquoted for single use and stored at -20 degrees Celsius; stability of aqueous solutions beyond 24 hours at room temperature has not been formally characterized in the published literature.

Handling does not require light protection under normal laboratory conditions. The compound is not classified as a controlled substance in any jurisdiction.

10. Stack Interactions and Combinations

CDD-0102 interacts with several drug classes through its M1 muscarinic receptor mechanism and through potential pharmacokinetic interactions. Investigators conducting research with CDD-0102, especially in combination protocols, should consider:

Acetylcholinesterase inhibitors: Concurrent administration of CDD-0102 with acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) produces additive cholinergic activity at M1 and other muscarinic receptors. The combination is pharmacologically rational for Alzheimer's disease research (the acetylcholinesterase inhibitor elevates endogenous acetylcholine while CDD-0102 provides additional direct M1 activation), but additive cholinergic adverse effects (salivation, gastrointestinal hypermotility, bradycardia) should be anticipated at higher doses of either component. The partial agonist character of CDD-0102 may partially buffer against excessive M1 activation in this combination.

Muscarinic antagonists: Concurrent administration with muscarinic antagonists (atropine, scopolamine, glycopyrrolate, benztropine, trihexyphenidyl) will attenuate or abolish the M1 agonist effects of CDD-0102. Scopolamine is used in research as a pharmacological challenge model for cholinergic cognitive deficit; CDD-0102 reversal of scopolamine-induced amnesia is a predictable and experimentally useful application [7].

Other muscarinic agonists: Concurrent use with other muscarinic agonists (xanomeline, pilocarpine, carbachol, cevimeline) produces additive muscarinic activation. The combination may exceed the adverse-effect threshold at each receptor subtype and is not recommended in preclinical protocols unless the interaction is the specific research question.

Antipsychotics with anticholinergic properties: Many first-generation and some second-generation antipsychotic agents (chlorpromazine, clozapine, olanzapine, quetiapine) have intrinsic muscarinic antagonist activity that may attenuate the M1

agonist effects of CDD-0102. Investigators studying CDD-0102 in the context of schizophrenia or autism models should consider the anticholinergic burden of concurrent antipsychotic medications.

QT-prolonging agents: CDD-0102 has not been reported to produce QT interval prolongation. However, formal cardiac safety pharmacology data have not been published, and caution with concurrent QT-prolonging agents is appropriate pending characterization.

Glutamatergic agents: Based on the glutamate-modulating activity observed in striatal circuits [13], CDD-0102 may interact with glutamatergic agents (memantine, ketamine, lamotrigine) through convergent effects on glutamate transmission. The direction and magnitude of the interaction would depend on the specific circuit and the relative doses.

11. Adverse Events and Safety

11.1 Preclinical adverse-event profile

The principal adverse event observed in preclinical studies is salivation, the cardinal peripheral cholinergic effect of muscarinic agonists. CDD-0102A produced salivation in mice at doses beginning at approximately 0.3 mg/kg intraperitoneally, with an estimated ED₅₀ for salivation of 2.0 mg/kg [11]. This compares favorably to xanomeline, which produces salivation at or near the cognitive-enhancing dose range. The safety margin between the minimum cognitive-enhancing dose (0.03 mg/kg for cognitive flexibility) and the salivation ED₅₀ (2.0 mg/kg) is approximately 67-fold, representing a substantial therapeutic window.

Other cholinergic adverse effects (lacrimation, diarrhea, urination, tremor) have not been reported at cognitive-enhancing doses in the published literature. At the 1.2 mg/kg dose used in the BTBR autism studies, CDD-0102A did not alter locomotor activity, body weight, or general health indicators over the experimental period [12, 13].

11.2 Acute toxicity

CDD-0102 exhibited a low acute toxicity profile in the Messer 2002 preclinical characterization [1]. Specific LD₅₀ values and maximum tolerated doses have not been published in the peer-reviewed literature; these data were generated as part of the NCATS BrIDGs IND-enabling program and were included in the IND application [2].

11.3 Genotoxicity and repeat-dose toxicology

Formal genotoxicity (Ames test, chromosomal aberration, micronucleus) and repeat-dose toxicology studies in rodent and non-rodent species were conducted through the NCATS BrIDGs program as components of the IND-enabling package [2]. Results have not been published. The successful IND filing indicates that these studies did not reveal findings that would preclude advancement to Phase 1 clinical testing.

11.4 Human safety data

No human safety data from Phase 1 or other clinical studies have been published as of the most recent monograph revision. The initiation of Phase 1 clinical testing, as reported by the NCATS BrIDGs program, implies that initial human safety and tolerability assessments were conducted, but results are not publicly available.

11.5 Class-effect safety considerations

As a muscarinic agonist, CDD-0102 carries the class-effect risk profile of cholinergic activation. The principal class-effect adverse events are salivation, gastrointestinal hypermotility (nausea, vomiting, diarrhea, abdominal cramping), diaphoresis (sweating), bradycardia, miosis, and bronchospasm [18]. These adverse events reflect activation of M2 receptors (bradycardia), M3 receptors (salivation, gastrointestinal effects, bronchospasm), and M2/M3 receptors (diaphoresis) in the periphery. The functional selectivity of CDD-0102 for M1 over M2 and M3 is the principal basis for the expectation of a more favorable adverse-event profile relative to the first-generation M1-preferring agonists, but this expectation has not been confirmed in human clinical data.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five M1 muscarinic receptor agonist candidates against CDD-0102, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical or preclinical), and overall validation. The five candidates were selected as the principal M1 muscarinic agonists with substantive clinical pharmacology programs in cognitive applications, with priority given to those that have produced material clinical evidence and that share the Alzheimer's disease positioning of CDD-0102.

12.1 Xanomeline

Mechanism: Non-selective muscarinic receptor agonist with preferential activity at M1 and M4 subtypes. Functional agonist activity is present at all five muscarinic subtypes, with highest potency at M1 and M4 [18, 23]. The M1/M4 co-agonism is now understood as the basis for both the cognitive-enhancing and antipsychotic properties of the compound.

Development trajectory: Eli Lilly developed xanomeline through Phase 3 clinical trials for Alzheimer's disease in the 1990s. A 343-patient Phase 3 trial (Bodick et al. 1997) demonstrated significant improvement on ADAS-Cog and CIBIC-plus at 75 mg three times daily, but the study was limited by high dropout rates (approximately 50 percent) attributable to cholinergic adverse events (nausea, vomiting, diarrhea, sweating, salivation) [23]. The Alzheimer's program was discontinued. Karuna Therapeutics (subsequently acquired by Bristol Myers Squibb) reformulated xanomeline in combination with trospium chloride (a peripherally restricted muscarinic antagonist) to address the peripheral adverse events, producing the combination KarXT. KarXT was approved by the FDA in September 2024 as Cobenfy for schizophrenia [21].

Novelty: Low as a standalone compound (developed in the 1980s). High as the xanomeline-trospium combination, which represents a novel strategy of pairing a central muscarinic agonist with a peripheral muscarinic antagonist.

Effect size: In the Alzheimer's Phase 3 trial, xanomeline produced a 3.5-point improvement on ADAS-Cog over placebo, a moderate effect size for cholinergic therapy [23]. As Cobenfy in schizophrenia, the PANSS total score reduction was -9.6 points over placebo (Cohen's $d = 0.61$), a substantial effect [21].

Promising potential: Very high as xanomeline-trospium (Cobenfy), which is FDA-approved and in commercial launch. Low as a standalone agent for Alzheimer's disease.

Side-effect profile: As a standalone agent, severe cholinergic adverse events at therapeutic doses (nausea 30-40 percent, vomiting 20-30 percent, diarrhea 15-25 percent, sweating 15-20 percent, salivation 10-15 percent) [23]. As Cobenfy with trospium, the peripheral adverse events are substantially mitigated but not eliminated (nausea, constipation, indigestion remain common) [21].

Overall validation: Very high. The muscarinic agonist mechanism has been validated at the level of FDA approval for a psychiatric indication. The Alzheimer's data provide proof of concept for cognitive enhancement through muscarinic agonism.

Comparison to CDD-0102: Xanomeline is the most clinically validated muscarinic agonist in the comparator panel but lacks the M1 functional selectivity of CDD-0102. The xanomeline-trospium strategy addresses peripheral adverse events through pharmacological antagonism (adding a second drug) rather than through intrinsic receptor-level selectivity (the CDD-0102 approach). CDD-0102 has the theoretical advantage of achieving tolerability with a single agent, but the clinical validation of this approach is absent. Xanomeline has the substantial advantage of FDA-approved status (as Cobenfy) and a large clinical evidence base.

12.2 Sabcomeline (SB-202026)

Mechanism: M1-preferring muscarinic partial agonist developed by SmithKline Beecham (now GlaxoSmithKline). Partial agonist activity at M1, with agonist or partial agonist activity at M2 and M3 at higher concentrations [19, 24].

Development trajectory: Advanced through Phase 2 clinical trials for Alzheimer's disease. Phase 2 trials demonstrated cognitive improvement on some endpoints but were limited by cholinergic adverse events at doses required for cognitive efficacy. The compound was also studied for effects on acetylcholine and

dopamine efflux in rat brain, showing increased acetylcholine efflux in medial pre-frontal cortex [24]. Clinical development was discontinued following the adverse-event signal and the modest cognitive effect sizes.

Novelty: Low. The M1-preferring partial agonist mechanism is shared with CDD-0102, though sabcomeline has less M1 selectivity.

Effect size: Modest cognitive improvement in Phase 2 Alzheimer's trials; insufficient effect size at tolerable doses to support Phase 3 advancement.

Promising potential: Very low. Development discontinued. The compound is available as a research tool from chemical suppliers.

Side-effect profile: Cholinergic adverse events (salivation, sweating, gastrointestinal disturbance) at doses approaching cognitive efficacy, reflecting insufficient M1/M3 selectivity [19, 24].

Overall validation: Low to moderate. Phase 2 clinical data provide some validation of the muscarinic agonist concept for cognition but do not support this specific compound.

Comparison to CDD-0102: CDD-0102 has greater M1 functional selectivity and a wider safety margin between cognitive-enhancing and adverse-effect doses in pre-clinical models. Sabcomeline has the advantage of Phase 2 human clinical data, which CDD-0102 lacks in published form. Both compounds represent partial agonist approaches to M1 activation, but CDD-0102's tetrahydropyrimidine-oxadiazole scaffold appears to confer superior functional selectivity.

12.3 Talsaclidine (WAL 2014 FU)

Mechanism: M1-preferring muscarinic agonist developed by Boehringer Ingelheim. Functional agonist activity at M1 with agonist activity at other subtypes at higher concentrations [20, 25].

Development trajectory: Advanced through Phase 2 clinical trials for Alzheimer's disease. Two Phase 2 studies demonstrated biochemical effects (reduction of Aβ in cerebrospinal fluid, consistent with M1-mediated alpha-secretase activation) but failed to demonstrate significant cognitive improvement on ADAS-Cog [20, 25]. Doses were limited by cholinergic adverse effects, particularly sweating and salivation. Clinical development was discontinued.

Novelty: Low. The M1-preferring agonist mechanism is conventional.

Effect size: Significant biochemical effect (CSF Abeta reduction) but non-significant cognitive effect at tolerable doses [25].

Promising potential: Very low. Development discontinued. The compound is available as a research tool.

Side-effect profile: Dose-limiting sweating and salivation at doses approaching cognitive efficacy [20, 25].

Overall validation: Moderate for the biochemical biomarker (CSF Abeta reduction, supporting the M1-alpha-secretase-APP hypothesis). Low for the cognitive endpoint.

Comparison to CDD-0102: CDD-0102 shares the M1-mediated sAPPalpha/APP-processing mechanism with talsaclidine but has greater functional selectivity for M1 and a correspondingly wider safety margin. The talsaclidine CSF Abeta data provide important validation of the disease-modifying hypothesis that CDD-0102 also targets. CDD-0102 lacks human biomarker data to confirm that its M1 activation produces the same CSF Abeta reduction at tolerable doses.

12.4 AF267B (NGX267)

Mechanism: M1 muscarinic agonist of the pyridine structural class, developed by Abraham Fisher and colleagues at the Israel Institute for Biological Research and advanced by Torrey Pines Therapeutics (subsequently acquired by Raptor Pharmaceutical). Functional agonist activity at M1 with selectivity over M2 and M3 [26, 27].

Development trajectory: Extensive preclinical pharmacology in Alzheimer's disease models, including demonstration of reduced Abeta production, reduced tau hyperphosphorylation, and cognitive improvement in transgenic mouse models of Alzheimer's disease [26, 27]. AF267B advanced to Phase 1 clinical evaluation for Alzheimer's disease but did not advance to Phase 2; the development program was discontinued following corporate restructuring at Torrey Pines/Raptor.

Novelty: Moderate. AF267B was one of the first M1 agonists to demonstrate combined anti-amyloid and anti-tau effects in preclinical models, a dual disease-modifying profile that was novel at the time of publication.

Effect size: Substantial in preclinical transgenic Alzheimer's models (reduction of Abeta pathology, reduction of tau hyperphosphorylation, cognitive improvement) [26, 27]. No Phase 2 human cognitive data.

Promising potential: Low. Development discontinued. The compound is available as a research tool.

Side-effect profile: Preclinical data suggest a favorable safety margin similar to CDD-0102, with M1 selectivity reducing peripheral cholinergic adverse events relative to xanomeline and sabcomeline [26].

Overall validation: Moderate. Strong preclinical evidence base with dual anti-amyloid and anti-tau effects. Phase 1 human safety data (not published in detail). No Phase 2 efficacy data.

Comparison to CDD-0102: AF267B and CDD-0102 occupy similar positions in the M1 muscarinic agonist development landscape: both are M1-selective agonists with strong preclinical profiles, both advanced to early clinical evaluation, and neither has produced published Phase 2 or later clinical data. AF267B has the advantage of more detailed published preclinical characterization of anti-amyloid and anti-tau effects in transgenic models. CDD-0102 has the advantage of more detailed published behavioral pharmacology in cognitive flexibility and autism-relevant endpoints.

12.5 Cevimeline (AF102B, Evoxac)

Mechanism: M1/M3 muscarinic agonist of the quinuclidine structural class, developed by Snow Brand Milk Products (Japan) and Daiichi Pharmaceutical, licensed to Evamist/Daiichi Sankyo. Functional agonist activity at M1 and M3 subtypes [28, 29].

Development trajectory: Originally developed as a cognitive enhancer for Alzheimer's disease, cevimeline advanced through clinical evaluation for that indication but was not approved for cognition. The compound was subsequently developed and approved by the FDA (2000) for the treatment of dry mouth (xerostomia) associated with Sjogren's syndrome, exploiting the M3-mediated salivary gland stimulation that was an adverse effect in the Alzheimer's trials [28]. Cevimeline is the only M1 muscarinic agonist from the Alzheimer's development era to achieve FDA approval, albeit for a non-cognitive indication.

Novelty: Low for the muscarinic agonist mechanism. Moderate for the repurposing from cognition to xerostomia.

Effect size: Non-significant cognitive effect at tolerable doses in Alzheimer's trials. Significant effect on salivary flow in Sjogren's syndrome [28].

Promising potential: Low for cognitive applications. Moderate as a marketed medicine for xerostomia (commercially available, generic competition).

Side-effect profile: Cholinergic adverse events including sweating, nausea, and rhinitis are common at therapeutic doses for xerostomia, reflecting M3 agonist activity [28]. These adverse events would be dose-limiting in a cognitive indication.

Overall validation: High as a marketed medicine (for xerostomia). Low for the cognitive application.

Comparison to CDD-0102: CDD-0102 has substantially greater M1 selectivity and correspondingly less M3 activity than cevimeline. The cevimeline clinical experience illustrates both the challenges and the opportunities of muscarinic agonist development: the M3-mediated salivation that was an adverse effect in cognitive trials became the therapeutic effect in the xerostomia indication. CDD-0102's functional selectivity for M1 over M3 would be expected to reduce the salivation signal but would also preclude the xerostomia application. The two compounds are complementary illustrations of the role of subtype selectivity in determining the therapeutic and adverse-effect profiles of muscarinic agonists.

12.6 Comparator summary

The five comparator compounds span the spectrum of M1 muscarinic agonist development from the 1990s to the present. **Xanomeline** is the most clinically validated compound in the panel, with FDA approval (as Cobenfy, in combination with trospium) for schizophrenia and Phase 3 Alzheimer's data demonstrating cognitive efficacy limited by adverse events; it represents the highest validation of the muscarinic agonist mechanism but achieves tolerability through the addition of a peripheral antagonist rather than through intrinsic M1 selectivity. **Sabcomeline** and **talsaclidine** are Phase 2 compounds that demonstrated modest cognitive signals limited by cholinergic adverse events; both illustrate the failure mode of first-generation M1-preferring agonists with insufficient subtype selectivity. **AF267B** is the most pharmacologically similar comparator to CDD-0102, sharing the M1-selective agonist profile and the dual cognitive-enhancing and anti-amyloid preclinical data,

but did not advance past Phase 1 due to corporate factors rather than pharmacological failure. **Cevimeline** achieved FDA approval for a non-cognitive indication (xerostomia) through exploitation of its M3 agonist activity.

CDD-0102 occupies a distinctive position in this comparator landscape as the compound with the most rigorously characterized functional selectivity for M1 in published preclinical data, the widest published safety margin between cognitive-enhancing and adverse-effect doses, and the most recent expansion of the pharmacological profile to non-Alzheimer's applications (autism-relevant behaviors, striatal glutamate modulation). Its principal limitation is the absence of published clinical data; the IND filing and Phase 1 initiation through the NCATS BrIDGs program are documented but results are not publicly available. The comparator landscape has been transformed by the 2024 FDA approval of xanomeline-trospium (Cobenfy), which validates the muscarinic agonist mechanism for a psychiatric indication and provides a clinical benchmark against which all subsequent M1 muscarinic agonist candidates will be evaluated.

The practical question for the positioning of CDD-0102 is whether intrinsic functional selectivity (the CDD-0102 approach) or pharmacological antagonist pairing (the xanomeline-trospium approach) will prove superior for chronic cognitive applications in Alzheimer's disease and related conditions. The intrinsic selectivity approach has the theoretical advantage of single-agent simplicity and of avoiding the potential for central muscarinic antagonism by trospium at high doses. The antagonist-pairing approach has the practical advantage of validated clinical success and regulatory approval. Both approaches are scientifically valid, and CDD-0102 remains a relevant research tool and potential clinical candidate in this evolving landscape.

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