

RESEARCH MONOGRAPH . COMPOUND PROFILE

Blarcamesine

*An orally bioavailable
aminotetrahydrofuran derivative
developed by Anavex Life Sciences as a
sigma-1 receptor agonist with muscarinic
receptor co-activity, investigated for
disease modification in Alzheimer's
disease, Rett syndrome, Parkinson's
disease dementia, and other
neurodegenerative and
neurodevelopmental conditions.*

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ABSTRACT

Blarcamesine (ANAVEX 2-73; tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine) is a small-molecule sigma-1 receptor (SIGMAR1) agonist and mixed muscarinic acetylcholine receptor modulator that has advanced through Phase 2b/3 clinical development for early Alzheimer's disease, Phase 3 for adult Rett syndrome, Phase 2 for Parkinson's disease dementia, and Phase 2/3 for pediatric Rett syndrome. The compound was first characterized pharmacologically by Villard, Espallergues, Keller, Vamvakides, and Maurice (2011) as a novel aminotetrahydrofuran derivative with anti-amnesic and neuroprotective activity mediated through dual engagement of sigma-1 and muscarinic acetylcholine receptors. The sigma-1 receptor is an endoplasmic reticulum chaperone protein localized at mitochondria-associated endoplasmic reticulum membranes (MAMs) that modulates calcium homeostasis, endoplasmic reticulum stress responses, mitochondrial function, autophagy, and neuroinflammation. Activation of SIGMAR1 by blarcamesine restores cellular proteostasis, reduces oxidative stress through suppression of reactive oxygen species, and promotes neuroplasticity through downstream modulation of brain-derived neurotrophic factor and glutamate signaling. In preclinical models, blarcamesine has demonstrated anti-amnesic activity in scopolamine- and dizocilpine-induced learning impairment paradigms, neuroprotection in the amyloid-beta(25-35) peptide injection mouse model of Alzheimer's disease (blocking both cognitive impairment and hippocampal oxidative stress), amelioration of motor, sensory, and autonomic phenotypes in the Mecp2 mouse model of Rett syndrome, and dose-dependent sigma-1 receptor

occupancy confirmed by positron emission tomography with the selective ligand [18F]FTC-146. The pivotal ANAVEX2-73-AD-004 Phase 2b/3 randomized, double-blind, placebo-controlled trial enrolled 508 patients with early Alzheimer's disease across 52 centers in five countries and demonstrated that oral blarcamesine at 50 mg and 30 mg daily significantly slowed cognitive decline on the primary endpoint ADAS-Cog13 at 48 weeks (38.5% and 34.6% slowing versus placebo, respectively; $P = 0.021$ and $P = 0.026$) [1]. Co-primary analysis showed significant benefit on CDR-SB. Volumetric magnetic resonance imaging demonstrated significant reduction of whole brain atrophy by 37.6%, total grey matter atrophy by 63.5%, and lateral ventricular enlargement by 25.1% versus placebo. Plasma amyloid-beta 42/40 ratio increased significantly in the blarcamesine group ($P = 0.048$). Open-label extension data through four years of continuous treatment demonstrated sustained benefit on ADAS-Cog13 and ADCS-ADL, with a delayed-start analysis suggesting importance of early treatment initiation. The AVATAR Phase 3 trial in 33 adult patients with Rett syndrome (MECP2 mutation-positive) met primary (RSBQ AUC, $P = 0.037$; Cohen's $d = 1.91$) and secondary (ADAMS, $P = 0.010$; CGI-I, $P = 0.037$) efficacy endpoints on once-daily oral dosing of up to 30 mg [2]. A proof-of-concept Phase 2 trial in 132 patients with Parkinson's disease dementia showed dose-dependent cognitive improvement on the CDR computerized assessment system and improvement on MDS-UPDRS total score at 14 weeks [3]. The EXCELLENCE Phase 2/3 pediatric Rett syndrome trial in 92 patients showed numerical improvement in RSBQ but did not achieve statistical separation from placebo, possibly due to a high placebo response rate [4]. The safety profile across clinical programs is characterized by predominantly mild-to-moderate adverse events concentrated during the initial dose

titration period. The most common treatment-emergent adverse events are dizziness (approximately 36% of treated patients in the Alzheimer's disease program), confusional state (approximately 14%), balance disorder, and fatigue; these are generally transient (resolving within 7 to 11 days), manageable by titration schedule adjustment, and not associated with serious or life-threatening sequelae. No neuroimaging-related adverse events (such as amyloid-related imaging abnormalities) have been reported. Long-term safety data through four years of continuous dosing have not revealed new safety signals. The European Medicines Agency accepted a Marketing Authorization Application for blarcamesine in Alzheimer's disease in December 2024, but the Committee for Medicinal Products for Human Use issued a negative opinion in December 2025 on grounds of insufficient demonstration of efficacy in patients without SIGMAR1 gene mutations and concerns regarding tolerability-driven treatment discontinuation. The application was subsequently withdrawn in March 2026. This monograph reviews the chemistry, structural class, and synthesis of blarcamesine; the sigma-1 receptor and muscarinic receptor pharmacology; the pharmacokinetic profile including the ANAVEX19-144 metabolite; the preclinical evidence base across Alzheimer's, Rett syndrome, fragile X syndrome, and Parkinson's disease models; the full clinical evidence base; sourcing considerations; reconstitution and handling; stack interactions; adverse events; and a comparative assessment of five sigma-1 receptor-active compounds against blarcamesine on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Blarcamesine.

Development code: ANAVEX 2-73 (Anavex Life Sciences Corp.). The development code is the canonical identifier in the early preclinical pharmacology literature and the identifier under which the seminal Villard et al. (2011) characterization was published [5].

Chemical Abstracts Service registry numbers: 195615-83-9 (free base), 195615-84-0 (hydrochloride salt). The hydrochloride salt is the formulated material used in all clinical trials and in commercially available research-grade preparations.

UNII (Unique Ingredient Identifier): 9T210MMZ3F.

International Union of Pure and Applied Chemistry name: 1-(2,2-diphenyltetrahydrofuran-3-yl)-N,N-dimethylmethanamine. The compound is an aminotetrahydrofuran derivative bearing two phenyl substituents at the 2-position of the tetrahydrofuran ring and an N,N-dimethylaminomethyl group at the 3-position.

Other designations: AVex-73, AV2-73.

1.2 Structural class and chemistry

Blarcamesine is an aminotetrahydrofuran derivative. The structural class is characterized by a saturated five-membered oxygen heterocycle (tetrahydrofuran) bearing geminal diphenyl substitution at C-2 and a dimethylaminomethyl group at C-3. The compound is structurally distinct from classical sigma-1 receptor ligands (which are typically built on piperazine, morpholine, or spirocyclic scaffolds) and from the marketed muscarinic receptor ligands (which are typically built on tropane or piperidine scaffolds). The tetrahydrofuran core with geminal diphenyl substitution is a structural motif associated with the Anavex proprietary chemical series [5, 6].

Molecular formula: C₁₉H₂₃NO (free base); C₁₉H₂₄ClNO (hydrochloride salt).

Molecular weight: 281.40 g/mol (free base); 317.86 g/mol (hydrochloride salt).

Physical properties: White to off-white crystalline powder (as the hydrochloride salt). Soluble in water, methanol, and dimethyl sulfoxide. The hydrochloride salt is the preferred form for aqueous formulations and for oral capsule preparations.

Stereochemistry: Blarcamesine contains one stereocenter at C-3 of the tetrahydrofuran ring. The compound has been studied as the racemic mixture in the published preclinical and clinical literature. Investigators should confirm the stereochemical form of research-grade material through the vendor certificate of analysis or by independent chiral chromatographic analysis.

1.3 Synthesis

The published synthesis of blarcamesine proceeds through a multi-step route beginning with the construction of the 2,2-diphenyltetrahydrofuran ring system, followed by introduction of the aminomethyl substituent at the 3-position. The general synthetic approach involves cyclization of an appropriately substituted 1,4-diol or gamma-lactol precursor bearing two phenyl groups, followed by reductive amination or direct alkylation to install the dimethylamino group. The hydrochloride salt is prepared by treatment of the free base with hydrogen chloride in an appropriate solvent (diethyl ether or isopropanol) followed by recrystallization [5]. Detailed synthetic procedures are described in patent filings by Anavex Life Sciences (US Patent 11,103,506 and related filings). The compound is manufactured under current Good Manufacturing Practice conditions for clinical supply.

2. Abstract

Blarcamesine (ANAVEX 2-73) is a sigma-1 receptor (SIGMAR1) agonist and mixed muscarinic acetylcholine receptor modulator developed by Anavex Life Sciences Corp. for the treatment of neurodegenerative and neurodevelopmental disorders. The compound is an aminotetrahydrofuran derivative that binds the sigma-1 receptor with an IC₅₀ of approximately 860 nanomolar and engages muscarinic acetylcholine receptors in the low-micromolar range [5, 6]. The sigma-1 receptor is an endoplasmic reticulum chaperone protein localized at mitochondria-associated endoplasmic reticulum membranes that modulates calcium signaling between the endoplasmic reticulum and mitochondria, regulates the unfolded protein response, governs autophagy, and suppresses neuroinflammation through effects on NF-kappaB-mediated cytokine production. Blarcamesine activation of SIGMAR1 restores these homeostatic processes in disease-relevant neuronal and glial populations, providing a mechanistic basis for activity across multiple neurodegenerative conditions that share underlying deficits in proteostasis, mitochondrial function, and neuroinflammatory regulation.

The compound advanced through a comprehensive clinical program spanning Alzheimer's disease, Rett syndrome, Parkinson's disease dementia, and exploratory studies in fragile X syndrome, Angelman syndrome, and infantile spasms. The pivotal ANAVEX2-73-AD-004 Phase 2b/3 trial in 508 early Alzheimer's disease patients demonstrated statistically significant slowing of cognitive decline on the ADAS-Cog13 primary endpoint at 48 weeks for both the 50 mg (P = 0.021) and 30 mg (P = 0.026) dose groups, with concordant significant effects on CDR-SB and on volumetric MRI measures of brain atrophy [1]. Open-label extension data through four years demonstrated sustained treatment benefit. The AVATAR Phase 3 trial in adult Rett syndrome met primary and secondary efficacy endpoints with large effect sizes [2]. A proof-of-concept Phase 2 trial in Parkinson's disease dementia demonstrated dose-dependent cognitive improvement at 14 weeks with sustained benefit through a 48-week extension [3].

The safety profile is characterized by predominantly mild, transient adverse events concentrated during the titration phase, principally dizziness, confusional state, and fatigue. No amyloid-related imaging abnormalities, no QT prolongation signal, and no treatment-related deaths have been reported across the clinical pro-

grams. The European Medicines Agency accepted a Marketing Authorization Application for blarcamesine in Alzheimer's disease in December 2024; the CHMP issued a negative opinion in December 2025 citing insufficient demonstration of efficacy in the broader (non-SIGMAR1-mutant) population and tolerability concerns. The application was withdrawn in March 2026 [7].

This monograph reviews the complete pharmacology, pharmacokinetics, pre-clinical and clinical evidence, safety, and comparative positioning of blarcamesine within the sigma-1 receptor agonist class.

3. Discovery and Development History

3.1 Origin

Blarcamesine was developed within the Anavex chemical series of aminotetrahydrofuran derivatives designed as mixed sigma-1 receptor and muscarinic acetylcholine receptor ligands. The compound series originated from the work of Alexandre Vamvakides, who synthesized a family of tetrahydrofuran-based ligands with dual sigma and muscarinic receptor affinity profiles. ANAVEX 2-73 was selected from this series for further development on the basis of its balanced receptor affinity profile, oral bioavailability, and favorable preclinical toxicology.

3.2 Preclinical characterization

The seminal pharmacological characterization of ANAVEX 2-73 was published by Villard, Espallergues, Keller, Vamvakides, and Maurice in the Journal of Psychopharmacology in 2011 [5]. This report established that the compound binds sigma-1 and muscarinic acetylcholine receptors in the low-micromolar range, alleviates scopolamine-induced and dizocilpine (MK-801)-induced learning impairments in mice, and blocks amyloid-beta(25-35) peptide-induced cognitive impairment and hippocampal oxidative stress in a nontransgenic Alzheimer's disease mouse model. The neuroprotective activity was subsequently extended in a 2015 study by Lahmy, Bhatt, and colleagues demonstrating that ANAVEX 2-73 provides mitochondrial protection against amyloid-beta(25-35) toxicity through sigma-1 receptor-dependent mechanisms [6].

3.3 Clinical development timeline

Anavex Life Sciences initiated a Phase 1 clinical trial of blarcamesine in healthy volunteers in 2011 in Australia, establishing safety, tolerability, and preliminary pharmacokinetic parameters for oral and intravenous dosing. A Phase 2a adaptive crossover study in mild-to-moderate Alzheimer's disease patients (ANAVEX2-73-002) followed, providing dose-response, bioavailability, and exploratory cognitive and functional data [8]. The Phase 2a data supported advancement to the pivotal Phase 2b/3 program.

The AVATAR Phase 3 trial in adult Rett syndrome was initiated in 2019 and reported positive results in February 2022 [2]. The ANAVEX2-73-AD-004 Phase 2b/3 Alzheimer's disease trial was initiated in 2020 across 52 sites in five countries (the United States, Canada, Australia, Europe, and the Republic of Korea) and reported primary results in 2024, with full publication by Sabbagh et al. in the Journal of Prevention of Alzheimer's Disease in January 2025 [1]. The ANAVEX2-73-PDD-001 Phase 2 proof-of-concept trial in Parkinson's disease dementia enrolled 132 patients and reported positive results in 2022, with a 48-week open-label extension reporting sustained benefit in 2023 [3, 9]. The EXCELLENCE Phase 2/3 trial in pediatric Rett syndrome enrolled 92 patients and completed in 2024; the primary endpoint did not achieve statistical significance [4].

3.4 Regulatory trajectory

Anavex Life Sciences submitted a Marketing Authorization Application (MAA) to the European Medicines Agency for blarcamesine for the treatment of early Alzheimer's disease, which was accepted for review in December 2024. In December 2025, the CHMP recommended refusal of the marketing authorization on grounds that the submitted evidence did not sufficiently demonstrate efficacy in patients without SIGMAR1 gene mutations and that safety could not be adequately characterized due to a high rate of treatment discontinuation driven by central nervous system side effects [7]. Concerns regarding potential nitrosamine impurity formation in the drug product were also raised. Anavex requested a re-examination of the opinion but subsequently withdrew the application in March 2026 before the re-examination concluded. The compound is not approved for any indication in any jurisdiction as of the monograph preparation date. Clinical development continues for Rett syndrome, Parkinson's disease dementia, fragile X syndrome, Angelman syndrome, and infantile spasms.

4. Mechanism of Action

Blarcamesine is a multi-target ligand. Its principal molecular activities are agonism at the sigma-1 receptor (SIGMAR1), modulation of muscarinic acetylcholine receptors, and indirect effects on NMDA receptor signaling through sigma-1-mediated mechanisms. These activities operate through an integrated mechanism centered on the sigma-1 receptor's role as an endoplasmic reticulum chaperone protein.

4.1 Sigma-1 receptor agonism

The sigma-1 receptor is a 223-amino-acid, single-pass transmembrane chaperone protein localized predominantly at mitochondria-associated endoplasmic reticulum membranes (MAMs), the specialized contact zones between the endoplasmic reticulum and the outer mitochondrial membrane [10, 11]. At MAMs, SIGMAR1 forms a complex with the endoplasmic reticulum chaperone BiP (GRP78) and with the inositol 1,4,5-trisphosphate receptor type 3 (IP3R3), regulating calcium flux from the endoplasmic reticulum into the mitochondrial matrix through the voltage-dependent anion channel on the outer mitochondrial membrane.

Under conditions of endoplasmic reticulum stress (accumulation of misfolded proteins, calcium depletion, oxidative damage), SIGMAR1 dissociates from BiP, stabilizes IP3R3, and sustains calcium transfer to mitochondria at levels that support oxidative phosphorylation and ATP production without reaching the apoptotic threshold [10]. This chaperone activity is the molecular basis for the neuroprotective and cytoprotective effects attributed to sigma-1 receptor agonism.

Blarcamesine binds SIGMAR1 with an IC₅₀ of approximately 860 nanomolar, promoting the active (BiP-dissociated) conformation and enhancing the chaperone's ability to stabilize client proteins at MAMs and at the plasma membrane [5, 6]. The downstream consequences of SIGMAR1 activation by blarcamesine include:

(a) Restoration of calcium homeostasis between the endoplasmic reticulum and mitochondria, supporting mitochondrial bioenergetics and reducing apoptotic signaling.

(b) Suppression of endoplasmic reticulum stress through modulation of the unfolded protein response (UPR), specifically through effects on the IRE1, PERK, and ATF6 arms of the UPR.

(c) Enhancement of autophagy, the cellular process for degradation of damaged organelles and aggregated proteins. Sigma-1 receptor agonism promotes autophagosome formation and lysosomal fusion, a mechanism of particular relevance to proteinopathies characterized by accumulation of misfolded tau, alpha-synuclein, or other aggregation-prone proteins [12].

(d) Suppression of neuroinflammation through inhibition of NF-kappaB-mediated transcription of proinflammatory cytokines (tumor necrosis factor alpha, interleukin-1 beta, interleukin-6) in microglia and astrocytes. Sigma-1 receptor activation also promotes anti-inflammatory M2 polarization of microglia [13].

(e) Reduction of oxidative stress through enhancement of antioxidant enzyme expression and through the anti-apoptotic Bcl-2 pathway, which sigma-1 receptor agonists stimulate via reactive oxygen species-dependent transcriptional activation of nuclear factor kappaB [14].

(f) Modulation of ion channel trafficking to the plasma membrane, including potassium channels, voltage-gated sodium channels, and NMDA-type glutamate receptors. SIGMAR1 physically associates with these channel complexes and modulates their surface expression and gating properties [10].

4.2 Muscarinic acetylcholine receptor modulation

Blarcamesine binds muscarinic acetylcholine receptors (primarily the M1 subtype) with affinity in the low-micromolar range [5]. Muscarinic M1 receptors are the predominant postsynaptic muscarinic subtype in cortex and hippocampus and are directly involved in cholinergic neurotransmission, synaptic plasticity, and cognitive function. The muscarinic M1 activity of blarcamesine provides a complementary cholinergic mechanism to the sigma-1 receptor activity, potentially supporting cognitive function through direct modulation of cholinergic signaling in cortical and hippocampal circuits.

The relative contribution of muscarinic receptor engagement to the overall pharmacological profile of blarcamesine in vivo has not been fully dissected from the sigma-1 receptor contribution. Preclinical studies using selective sigma-1 receptor antagonists (NE-100, BD-1047) have demonstrated that the anti-amnesic activity of

blarcamesine is partially blocked by sigma-1 receptor antagonism, supporting a significant sigma-1 receptor-dependent component, while residual activity in the presence of sigma-1 antagonism is consistent with a muscarinic contribution [5].

4.3 NMDA receptor modulation

The sigma-1 receptor physically associates with the GluN1 subunit of the NMDA receptor at the plasma membrane and modulates NMDA receptor-mediated calcium influx and synaptic plasticity [10]. Blarcamesine, through sigma-1 receptor activation, indirectly modulates NMDA receptor function by enhancing receptor trafficking to the synapse and by modulating receptor gating properties. This mechanism provides a third pathway for cognitive enhancement and neuroprotection that is mechanistically distinct from direct NMDA receptor ligands such as memantine.

4.4 Composite pharmacology and transcriptomic evidence

Whole-blood transcriptomic analysis from the Phase 2b/3 Alzheimer's disease trial demonstrated that blarcamesine treatment modulates expression of genes within multiple neurodegenerative pathways, including the Alzheimer's disease pathway, oxidative phosphorylation, protein processing in the endoplasmic reticulum, autophagy, and neurotrophin signaling [15]. These transcriptomic findings are consistent with the multi-target mechanism of action and support the hypothesis that blarcamesine exerts disease-modifying effects through restoration of fundamental cellular homeostatic processes rather than through modulation of a single molecular target.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Blarcamesine is well absorbed after oral administration. The compound has been studied in oral capsule formulations (30 mg and 50 mg) and as an oral liquid formulation (up to 30 mg for Rett syndrome populations). The Phase 2a adaptive cross-over study in Alzheimer's disease patients administered oral doses of 30 mg and 50 mg and intravenous doses of 3 mg and 5 mg, allowing calculation of absolute oral bioavailability by comparison of oral and intravenous pharmacokinetic parameters [8]. Dose-proportional pharmacokinetics were observed across the studied dose range, indicating linear kinetics at clinically relevant doses.

5.2 Distribution

Blarcamesine demonstrates central nervous system penetration sufficient to achieve pharmacologically relevant sigma-1 receptor occupancy. Positron emission tomography (PET) studies using the highly selective sigma-1 receptor ligand [18F]FTC-146 and ex vivo autoradiographic studies have demonstrated dose-dependent sigma-1 receptor occupancy in brain tissue, confirming that oral dosing at the clinical dose range achieves meaningful target engagement in the central nervous system [16].

5.3 Metabolism

Blarcamesine undergoes hepatic metabolism. Steady-state plasma levels of both blarcamesine and its primary metabolite ANAVEX19-144 have been measured in clinical studies. The metabolite ANAVEX19-144 has been characterized in the clinical pharmacokinetic program; both parent compound and metabolite concentrations are monitored in clinical trials to characterize the metabolic disposition. Detailed cytochrome P450 isoform attribution has not been fully disclosed in the

public literature. Investigators should be aware of the potential for drug-drug interactions through hepatic cytochrome P450 pathways, although no clinically significant interactions have been identified in the clinical program to date.

5.4 Elimination

Pharmacokinetic parameters including elimination half-life, clearance, and renal excretion fraction have been characterized in the Phase 1 and Phase 2a clinical programs. Detailed numerical pharmacokinetic parameters remain within the proprietary clinical dataset. The convenient once-daily oral dosing regimen used across all clinical programs is consistent with a pharmacokinetic profile supporting once-daily administration.

5.5 Routes of administration

Two routes of administration have been used in clinical development: oral (capsules at 30 mg and 50 mg for adult indications; oral liquid at up to 30 mg for pediatric Rett syndrome) and intravenous (3 mg and 5 mg in the Phase 2a crossover study for bioavailability determination). Oral administration is the intended route for all therapeutic applications.

5.6 Special populations

Pediatric pharmacokinetics have been characterized in the EXCELLENCE Phase 2/3 Rett syndrome trial, which enrolled patients aged 5 through 17 years at a dose of 30 mg oral liquid once daily [4]. Geriatric pharmacokinetics are represented by the Alzheimer's disease and Parkinson's disease dementia populations (typical age range 50 to 85 years). Detailed population pharmacokinetic analyses by age, hepatic function, and renal function have not been published in the public literature.

5.7 Precision medicine and SIGMAR1 genotype

Analysis of the Phase 2a Alzheimer's disease study identified genomic biomarkers, including SIGMAR1 gene variants, that correlated with clinical response to blarcamesine [17]. Patients carrying specific SIGMAR1 variants showed enhanced treatment response, suggesting that SIGMAR1 genotype may serve as a precision medicine biomarker for patient selection. This finding was a central element of the

regulatory strategy for the European Medicines Agency submission and was the subject of the CHMP negative opinion, which concluded that efficacy in the broader (non-SIGMAR1-mutant) population was not adequately demonstrated.

6. Preclinical Pharmacology

6.1 Anti-amnesic activity

The Villard et al. (2011) study demonstrated that blarcamesine alleviates scopolamine-induced (cholinergic) and dizocilpine-induced (glutamatergic) learning impairments in mice at doses of 0.01 to 1 mg/kg administered intraperitoneally [5]. The anti-amnesic activity was observed across multiple behavioral paradigms including spontaneous alternation in the Y-maze, passive avoidance, and water maze tasks. The dose-response profile showed an inverted-U pattern at higher doses, characteristic of sigma-1 receptor agonists and consistent with receptor desensitization at supramaximal concentrations.

6.2 Neuroprotection in amyloid-beta models

When administered simultaneously with amyloid-beta(25-35) peptide by intracerebroventricular injection seven days before behavioral testing, blarcamesine blocked the appearance of learning impairments and prevented hippocampal oxidative stress (measured by lipid peroxidation and protein carbonylation markers) [5, 6]. A 2025 publication confirmed that blarcamesine prevents memory impairment and hippocampal injury in the amyloid-beta injection Alzheimer's disease model [18]. The neuroprotective activity was attenuated by the selective sigma-1 receptor antagonist NE-100, confirming sigma-1 receptor dependence.

6.3 Mitochondrial protection

Lahmy, Bhatt, and colleagues (2015) demonstrated that blarcamesine provides mitochondrial protection against amyloid-beta(25-35)-induced toxicity in a nontransgenic Alzheimer's disease model [6]. The compound prevented mitochondrial respiratory chain dysfunction and reduced markers of oxidative damage in hippocampal tissue. The mitochondrial protective mechanism is consistent with the sigma-1 receptor's role in calcium homeostasis at MAMs and in regulation of mitochondrial bioenergetics.

6.4 Rett syndrome models

Kaufmann et al. (2019) demonstrated that blarcamesine ameliorates neurologic impairments in the *Mecp2* heterozygous mouse model of Rett syndrome [19]. Administration to younger and older adult mice resulted in improvement across multiple motor, sensory, and autonomic phenotypes of relevance to Rett syndrome, including motor coordination and balance (rotarod performance), acoustic and visual startle responses, hindlimb clasping (a marker of neurological severity), and apnea in expiration (a cardinal autonomic feature of the disorder). The behavioral improvements were associated with increased sigma-1 receptor expression and with normalization of downstream molecular markers.

6.5 Fragile X syndrome models

Fisher et al. (2021) characterized the effects of blarcamesine in the *Fmr1* knockout mouse model of fragile X syndrome [16]. Doses that yielded measurable sigma-1 receptor occupancy (confirmed by PET with [18F]FTC-146) were effective for improving synaptic and behavioral phenotypes, including reduction of audiogenic seizure susceptibility, normalization of marble burying behavior, and improvement of prepulse inhibition. The study established a quantitative relationship between receptor occupancy and behavioral efficacy, supporting the sigma-1 receptor as the primary pharmacological target.

6.6 Tau hyperphosphorylation

Blarcamesine has been shown to block tau hyperphosphorylation in the amyloid-beta(25-35) injection model, acting through a mechanism dependent on both sigma-1 receptor and muscarinic receptor engagement [20]. The blockade of tau hyperphosphorylation provides a mechanistic link to disease modification in tauopathies and supports the relevance of the compound to the pathological cascade in Alzheimer's disease beyond amyloid-beta toxicity.

7. Clinical Evidence Base

7.1 Phase 2a Alzheimer's disease (ANAVEX2-73-002)

The Phase 2a adaptive two-period crossover study enrolled patients with mild-to-moderate Alzheimer's disease and administered oral blarcamesine (30 mg or 50 mg) and intravenous blarcamesine (3 mg or 5 mg) to characterize pharmacokinetics, bioavailability, and exploratory cognitive and functional endpoints [8, 17]. The study demonstrated linear dose-proportional pharmacokinetics, established the oral bioavailability of the compound, and identified SIGMAR1 gene variants as potential biomarkers of clinical response through an artificial intelligence-based precision medicine framework.

7.2 Phase 2b/3 Alzheimer's disease (ANAVEX2-73-AD-004)

The pivotal ANAVEX2-73-AD-004 trial was a randomized, double-blind, placebo-controlled, 48-week Phase 2b/3 study conducted across 52 medical research centers and hospitals in five countries [1]. A total of 508 participants with early Alzheimer's disease were randomized 2:1 to blarcamesine (n = 338; medium-dose group at 30 mg or high-dose group at 50 mg) or placebo (n = 170), administered as oral capsules once daily for 48 weeks.

Primary endpoint (ADAS-Cog13): Blarcamesine significantly slowed cognitive decline at 48 weeks. The 50 mg group showed a 38.5% reduction in clinical progression versus placebo (least-squares mean difference, -2.149; P = 0.021). The 30 mg group showed a 34.6% reduction versus placebo (least-squares mean difference, -1.934; P = 0.026).

Co-primary endpoint (CDR-SB): Significant benefit was demonstrated under the prespecified multiplicity control rule (P < 0.025 for both dose groups).

Co-primary endpoint (ADCS-ADL): Activities of daily living did not reach statistical significance at 48 weeks.

Neuroimaging biomarkers: Volumetric MRI demonstrated significant reduction of whole-brain atrophy by 37.6% ($P = 0.002$), total grey matter atrophy by 63.5%, and lateral ventricular enlargement by 25.1% in blarcamesine-treated patients versus placebo.

Plasma biomarkers: The plasma amyloid-beta 42/40 ratio increased significantly in the blarcamesine group versus placebo ($P = 0.048$), consistent with reduced amyloidogenic processing or enhanced amyloid clearance.

Open-label extension: Blarcamesine-treated patients continued to accrue benefit through up to four years of continuous treatment on ADAS-Cog13 and ADCS-ADL. A delayed-start analysis demonstrated that participants who initiated treatment earlier showed greater stability of cognitive function compared to those who delayed treatment by approximately one year, supporting a disease-modifying rather than purely symptomatic mechanism [21].

7.3 AVATAR Phase 3 adult Rett syndrome

The AVATAR trial was a randomized, double-blind, placebo-controlled Phase 3 study in 33 adult female patients with Rett syndrome confirmed by MECP2 gene mutation [2]. Patients received once-daily oral liquid blarcamesine at doses up to 30 mg or placebo.

Primary endpoint (RSBQ AUC): Statistically significant improvement in 72.2% of blarcamesine-treated patients versus 38.5% on placebo ($P = 0.037$). Cohen's d effect size was 1.91, considered very large.

Secondary endpoints: ADAMS (Anxiety, Depression, and Mood Scale) showed clinically meaningful and statistically significant reduction of emotional behavioral symptoms (52.9% versus 8.3% on placebo; $P = 0.010$). CGI-I (Clinical Global Impression-Improvement) showed significantly more patients achieving clinically meaningful response in the blarcamesine group (72.2% versus 38.5%; $P = 0.037$).

7.4 EXCELLENCE Phase 2/3 pediatric Rett syndrome

The EXCELLENCE study enrolled 92 pediatric patients with Rett syndrome aged 5 through 17 years and randomized them 2:1 to blarcamesine 30 mg oral liquid or placebo once daily [4]. Treatment with blarcamesine led to numerical improvement in RSBQ scores (average improvement of 12.93 points versus 8.32 points on

placebo), but the difference did not achieve statistical significance. A high placebo response rate was observed, possibly related to a slight imbalance in disease severity at baseline and the 2:1 randomization ratio. Safety data did not reveal new concerns. The trial result does not exclude a treatment effect but is considered inconclusive.

7.5 Phase 2 Parkinson's disease dementia (ANAVEX2-73-PDD-001)

The proof-of-concept Phase 2 randomized, double-blind, placebo-controlled trial enrolled 132 adults aged 50 to 85 years with Parkinson's disease dementia [3]. Participants were randomized to blarcamesine 30 mg, blarcamesine 50 mg, or placebo oral capsules once daily for 14 weeks.

Results showed clinically meaningful, dose-dependent, and statistically significant improvements on the Cognitive Drug Research (CDR) computerized assessment system. The difference on the MDS-UPDRS (Movement Disorder Society-Unified Parkinson's Disease Rating Scale) total score between the high-dose blarcamesine arm and placebo at 14 weeks was -14.51 points [3].

The 48-week open-label extension (ANAVEX2-73-PDD-EP-001) demonstrated sustained longitudinal beneficial effects on prespecified primary and secondary endpoints, with blarcamesine treatment generally safe and well tolerated [9].

7.6 Exploratory indications

Blarcamesine is in Phase 2/3 clinical development for fragile X syndrome, Phase 1 for Angelman syndrome, and Phase 1 for infantile spasms. These early-stage programs are supported by preclinical evidence of sigma-1 receptor-mediated correction of synaptic and behavioral phenotypes in the respective animal models.

8. Sourcing and Quality Verification

Blarcamesine is not an approved pharmaceutical product in any jurisdiction. The compound is available as a research-grade preparation from multiple chemical and pharmaceutical research suppliers.

Research-grade blarcamesine hydrochloride is supplied by MedChemExpress, Selleckchem, TargetMol, MedKoo Biosciences, ChemicalBook, Sun-shinechem, and other specialty chemical vendors at greater than 98% purity by HPLC. Supply is typically in milligram quantities (5 mg to 100 mg) as the hydrochloride salt. Pricing varies by vendor and quantity, generally in the range of \$100 to \$500 per 10 mg of research-grade material.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98%
- Mass spectrometry confirmation of molecular weight (282.40 +/- 0.01 for the protonated free base [M+H]⁺; 318.86 for the hydrochloride)
- Nuclear magnetic resonance spectroscopy (¹H and ¹³C) for structural confirmation
- Residual solvent analysis (gas chromatography of synthesis solvents)
- Certificate of analysis review from the vendor, including characterization of the stereochemical form

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade blarcamesine market is established but the compound is less widely sourced than marketed pharmaceuticals, and on-receipt analytical confirmation is appropriate for all investigations.

9. Reconstitution and Handling

Blarcamesine hydrochloride is soluble in water and in dimethyl sulfoxide (DMSO). For in vitro research applications, stock solutions are typically prepared at 10 mM to 100 mM in DMSO, stored in aliquots at -20 degrees Celsius, and diluted to working concentrations in cell culture medium or assay buffer immediately before use. Aqueous stock solutions can be prepared for in vivo research at concentrations appropriate to the dosing volume and route.

The compound should be stored as a dry powder at -20 degrees Celsius, protected from moisture and light, under which conditions it is stable for at least two years according to vendor specifications. Reconstituted DMSO stock solutions are stable at -20 degrees Celsius for at least six months; repeated freeze-thaw cycles should be minimized through single-use aliquoting.

For oral administration in research settings, the compound can be dissolved in appropriate vehicles (water, saline, or oral gavage vehicles such as methylcellulose suspensions) at the time of dosing. The clinical formulations used in the Anavex trials are oral capsules (30 mg and 50 mg) and oral liquid, which are proprietary clinical supply and not commercially available.

10. Stack Interaction Considerations

Blarcamesine interacts with several drug classes through its sigma-1 receptor and muscarinic receptor pharmacology. Investigators conducting research with blarcamesine, especially in combination protocols, should consider:

Acetylcholinesterase inhibitors: Concurrent donepezil, rivastigmine, or galantamine produces additive cholinergic activity through distinct mechanisms (cholinesterase inhibition plus muscarinic receptor modulation). This combination is pharmacologically rational for Alzheimer's disease research and was permitted in the Phase 2b/3 Alzheimer's disease trial, where most patients were on stable background acetylcholinesterase inhibitor therapy. Additive parasympathomimetic adverse events (nausea, diarrhea) should be monitored.

Memantine: Concurrent memantine (an NMDA receptor antagonist) and blarcamesine (which indirectly modulates NMDA receptor function through sigma-1-mediated mechanisms) represents a mechanistically complementary combination. Memantine was permitted as background therapy in the Phase 2b/3 trial. No characterized pharmacokinetic interaction has been identified.

Sigma-1 receptor antagonists: Concurrent administration of sigma-1 receptor antagonists (NE-100, BD-1047, haloperidol at high doses) would attenuate the pharmacological activity of blarcamesine. Haloperidol binds sigma-1 receptors with submicromolar affinity and may function as a sigma-1 antagonist at clinical doses; co-administration in research should be interpreted with this pharmacological consideration.

SSRIs with sigma-1 receptor activity: Fluvoxamine is a potent sigma-1 receptor agonist (K_i approximately 36 nM, substantially higher affinity than blarcamesine). Concurrent fluvoxamine and blarcamesine would produce additive sigma-1 receptor activation; the combination has not been studied and may approach the receptor activation ceiling.

Other sigma-1 receptor agonists: Concurrent administration with pridopidine, cutamesine (SA4503), or other sigma-1 agonists would produce additive or redundant receptor activation. Combination studies have not been conducted.

Anticholinergic agents: Concurrent anticholinergic drugs (oxybutynin, benztropine, diphenhydramine, tricyclic antidepressants) may counteract the muscarinic receptor-mediated component of blarcamesine activity. The combination is not pharmacologically rational for cognitive applications.

Hepatic enzyme inhibitors and inducers: Given that blarcamesine undergoes hepatic metabolism, strong CYP inhibitors and inducers may alter exposure. Specific CYP isoform dependencies have not been fully disclosed; investigators should exercise caution with strong CYP3A4 and CYP2D6 inhibitors until metabolic pathways are clarified.

11. Adverse Events and Safety

11.1 Common adverse events

The safety database for blarcamesine spans the Phase 2b/3 Alzheimer's disease trial (n = 508), the AVATAR Phase 3 Rett syndrome trial (n = 33), the Phase 2 Parkinson's disease dementia trial (n = 132), the EXCELLENCE Phase 2/3 pediatric Rett syndrome trial (n = 92), and earlier Phase 1 and Phase 2a studies. The aggregate safety profile is characterized by:

- Dizziness (approximately 36% in the Alzheimer's disease program; the most common adverse event; predominantly mild, Grade 1 or 2; transient, resolving within approximately 7 to 11 days; concentrated during the initial dose titration period)
- Confusional state (approximately 14% in the Alzheimer's disease program)
- Balance disorder (less common; mild)
- Fatigue (mild to moderate)
- Headache (less common)

These adverse events were predominantly linked to the initial titration phase and could be managed with adjusted titration schedules and dosing time optimization. The adverse event profile across the Rett syndrome and Parkinson's disease dementia programs was consistent with that observed in the Alzheimer's disease program.

11.2 Serious adverse events

In the Phase 2b/3 Alzheimer's disease trial, participants with at least one serious treatment-emergent adverse event comprised 16.7% of the blarcamesine group and 10.1% of the placebo group. No severe or life-threatening adverse events were attributed to blarcamesine. There were no treatment-related deaths across any clinical program.

11.3 Neuroimaging safety

No amyloid-related imaging abnormalities (ARIA-E or ARIA-H), which are associated with anti-amyloid antibody therapies (lecanemab, aducanumab), have been reported with blarcamesine. This absence of neuroimaging-related adverse events distinguishes blarcamesine from the anti-amyloid monoclonal antibody class.

11.4 Cardiac safety

No QT interval prolongation signal has been identified in the clinical program. Electrocardiographic monitoring in the Phase 2b/3 Alzheimer's disease trial did not reveal clinically significant changes over 48 weeks of treatment.

11.5 Long-term safety

Continuous blarcamesine treatment for up to four years in the open-label extension of the Alzheimer's disease trial demonstrated a good comparative safety profile. No new safety findings, no notable vital sign changes, no clinically significant laboratory abnormalities, and no pattern of serious adverse events were observed over the long-term follow-up period [21].

11.6 Tolerability and discontinuation

The CHMP negative opinion cited concerns about the proportion of patients who discontinued treatment due to central nervous system adverse events during the Phase 2b/3 trial [7]. Investigators should be aware that the titration phase is the period of highest risk for tolerability-driven discontinuation and that conservative titration schedules may improve retention.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five sigma-1 receptor-active compounds against blarcamesine, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as sigma-1 receptor ligands with substantive clinical or preclinical pharmacology programs, with priority on those with clinical evidence in neurodegenerative or cognitive applications.

12.1 Pridopidine (ACR16, Huntexil)

Mechanism: Highly selective sigma-1 receptor agonist. Pridopidine was initially characterized as a dopamine D2 receptor ligand ("dopamine stabilizer") but PET occupancy studies demonstrated that at behaviorally and clinically active doses, pridopidine predominantly occupies sigma-1 receptors with negligible D2 receptor occupancy [22].

Development trajectory: Teva Pharmaceutical and subsequently Prilenia Therapeutics developed pridopidine through Phase 2 and Phase 3 trials for Huntington's disease. The PRIDE-HD Phase 2 trial in 397 Huntington's disease patients did not meet its primary endpoint (Total Motor Score on the UHDRS) but showed positive signals on the Total Functional Capacity (TFC) endpoint at the 45 mg twice-daily dose [23]. PROOF-HD Phase 3 trial results have been reported; the compound continues in development for Huntington's disease and for amyotrophic lateral sclerosis.

Novelty: Moderate. Pridopidine was originally positioned as a dopamine stabilizer; its repositioning as a selective sigma-1 receptor agonist represents a conceptual advance but the receptor mechanism is established.

Effect size: Mixed. Primary motor endpoints in Huntington's disease have not been met; functional capacity signals are modest. Preclinical neuroprotective effects are robust.

Promising potential: Moderate. Development continues for Huntington's disease and ALS, but Phase 3 results in Huntington's disease have been mixed.

Side-effect profile: Well tolerated in Phase 2 and Phase 3 studies. Common adverse events include nasopharyngitis, insomnia, and falls (in the Huntington's disease population). No severe safety signals.

Overall validation: Moderate. Extensive clinical development with mixed efficacy results. The compound serves as the principal selective sigma-1 receptor agonist reference in the clinical literature.

Comparison to blarcamesine: Pridopidine is more selective for sigma-1 over other targets than blarcamesine (which has muscarinic co-activity). Blarcamesine has produced more robust cognitive endpoints (ADAS-Cog13 significance in Alzheimer's disease) while pridopidine has produced functional capacity signals in Huntington's disease. The two compounds target different disease populations with different outcome measures, making direct efficacy comparison difficult. Blarcamesine's dual sigma-1/muscarinic mechanism may confer advantages for cognitive indications specifically.

12.2 Cutamesine (SA4503)

Mechanism: Potent and highly selective sigma-1 receptor agonist. K_i for sigma-1 receptor is approximately 17 nM, substantially more potent than blarcamesine (IC_{50} approximately 860 nM) [24].

Development trajectory: Developed by Santen Pharmaceutical and M's Science for ischemic stroke recovery. A Phase 2 clinical trial in patients with ischemic stroke (SA4503 administered at 1 mg/day for 28 days) did not demonstrate significant improvement in functional recovery compared to placebo [25]. The compound was not advanced to Phase 3.

Novelty: Low. The mechanism is conventional selective sigma-1 receptor agonism.

Effect size: Non-significant in stroke recovery. Robust preclinical effects on cognitive impairment in scopolamine and PCP models.

Promising potential: Low. Clinical development has stalled following the negative Phase 2 stroke trial.

Side-effect profile: Generally well tolerated in Phase 2. No material safety concerns were reported.

Overall validation: Low. Negative Phase 2 stroke trial. Persists as a research tool for sigma-1 receptor pharmacology.

Comparison to blarcamesine: Cutamesine is substantially more potent at sigma-1 receptors than blarcamesine but has not demonstrated clinical efficacy in any indication. Blarcamesine's mixed sigma-1/muscarinic mechanism and the broader clinical development program (multiple indications, multiple Phase 2 and Phase 3 trials with positive signals) position it substantially ahead of cutamesine in clinical translation.

12.3 Fluvoxamine

Mechanism: Selective serotonin reuptake inhibitor (SSRI) with potent sigma-1 receptor agonism. Among the SSRIs, fluvoxamine has the highest affinity at sigma-1 receptors (K_i approximately 36 nM), substantially higher than blarcamesine [26]. The compound's clinical profile is dominated by SSRI activity (serotonin reuptake inhibition), with the sigma-1 receptor agonism representing a secondary pharmacological mechanism.

Development trajectory: Fluvoxamine is an approved and widely marketed SSRI for obsessive-compulsive disorder and depression. It has been studied in research settings for delirium in Alzheimer's disease patients (where sigma-1 receptor agonism is hypothesized to contribute to the therapeutic effect) and for cognitive enhancement [26, 27].

Novelty: Low. The compound is an established SSRI with incidental sigma-1 receptor activity.

Effect size: Modest in delirium and cognitive studies. The cognitive effects are difficult to dissect from the SSRI mechanism.

Promising potential: Not applicable as a sigma-1 receptor-specific candidate. The compound is approved and marketed for other indications.

Side-effect profile: Well-characterized SSRI adverse-event profile (nausea, somnolence, sexual dysfunction, serotonin syndrome risk). The adverse events are dominated by the SSRI mechanism rather than by sigma-1 receptor activation.

Overall validation: High as an SSRI. Low as a sigma-1 receptor-specific candidate.

Comparison to blarcamesine: Fluvoxamine has substantially higher sigma-1 receptor affinity but its pharmacological profile is dominated by serotonin reuptake inhibition, making it unsuitable as a pure sigma-1 receptor tool. Blarcamesine's profile, centered on sigma-1 receptor agonism with muscarinic co-activity and without serotonergic reuptake inhibition, is more pharmacologically coherent for sigma-1 receptor-mediated indications.

12.4 ANAVEX 3-71 (AF710B)

Mechanism: Mixed muscarinic M1 receptor agonist, sigma-1 receptor agonist, and M2/M4 muscarinic antagonist. ANAVEX 3-71 is a more muscarinic-weighted member of the Anavex chemical series compared to blarcamesine and has a distinct selectivity profile with direct M1 agonist activity and allosteric modulation properties [28].

Development trajectory: Anavex Life Sciences advanced ANAVEX 3-71 through preclinical development for Alzheimer's disease and frontotemporal dementia. A Phase 1 clinical trial was completed. The compound has demonstrated reduction of amyloid-beta and tau pathology markers in transgenic Alzheimer's disease mouse models [28].

Novelty: Moderate to high. The triple mechanism (M1 agonist, sigma-1 agonist, M2/M4 antagonist) is distinctive within the sigma-1 receptor pharmacology space.

Effect size: Preclinical only. Robust reduction of pathological markers in transgenic mouse models, but no clinical efficacy data beyond Phase 1.

Promising potential: Low to moderate. Early-stage clinical development. The compound is the pipeline candidate behind blarcamesine within the Anavex portfolio.

Side-effect profile: Phase 1 safety has been reported as acceptable. No material safety concerns in human dosing to date.

Overall validation: Low. Preclinical and Phase 1 only.

Comparison to blarcamesine: ANAVEX 3-71 is the more muscarinic-weighted sibling compound to blarcamesine within the Anavex series. Blarcamesine is substantially further in clinical development (Phase 2b/3 with published efficacy data versus Phase 1). The two compounds may serve complementary roles in future research: blarcamesine as the sigma-1-weighted candidate for cognitive and neurodegenerative indications, and ANAVEX 3-71 as the muscarinic-weighted candidate for pathology modification.

12.5 Dextromethorphan (as sigma-1 receptor agonist)

Mechanism: Sigma-1 receptor agonist (K_i approximately 200 nM), NMDA receptor antagonist, serotonin and norepinephrine reuptake inhibitor, and voltage-gated sodium channel blocker [29]. Dextromethorphan is a multi-target ligand with sigma-1 receptor agonism as one of several pharmacological activities. The FDA-approved combination of dextromethorphan with quinidine (Nuedexta) for pseudobulbar affect and the combination with bupropion (Auvelity) for major depressive disorder exploit the NMDA receptor antagonism and sigma-1 receptor agonism in combination.

Development trajectory: Dextromethorphan is an approved over-the-counter antitussive with a long clinical history. The sigma-1 receptor agonist activity has been exploited in research for neuroprotection and in the approved combination products for neuropsychiatric indications. The compound has been studied in Alzheimer's disease (AVP-786, dextromethorphan/quinidine, Phase 3 for agitation) with mixed results.

Novelty: Low. The compound is an established multi-target agent with incidental sigma-1 receptor activity.

Effect size: Modest in neuropsychiatric applications. The contribution of sigma-1 receptor agonism to the overall effect is difficult to dissect from NMDA receptor antagonism and monoamine reuptake effects.

Promising potential: Moderate in combination products for neuropsychiatric indications. Not positioned as a sigma-1 receptor-specific candidate.

Side-effect profile: Well characterized. Common adverse events include dizziness, nausea, and somnolence. CYP2D6-mediated metabolism produces variable exposure in extensive versus poor metabolizers (addressed by quinidine co-administration in Nuedexta and by bupropion co-administration in Auvelity).

Overall validation: High as a multi-target agent. Low as a sigma-1 receptor-specific candidate.

Comparison to blarcamesine: Dextromethorphan has higher sigma-1 receptor affinity than blarcamesine but its pharmacological profile is dominated by NMDA receptor antagonism and monoamine reuptake inhibition. Blarcamesine offers a more pharmacologically coherent sigma-1 receptor-centered mechanism for investigating SIGMAR1-dependent disease modification. The two compounds are not direct comparators for sigma-1-specific applications.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the sigma-1 receptor pharmacology space. **Pridopidine** is the most selective sigma-1 receptor agonist in clinical development, with extensive Huntington's disease data but mixed primary endpoint results. **Cutamesine** is a potent selective agonist that failed in Phase 2 stroke trials. **Fluvoxamine** is an approved SSRI with incidental sigma-1 activity, unsuitable as a sigma-1-specific tool. **ANAVEX 3-71** is a muscarinic-weighted sibling compound to blarcamesine at an early clinical stage. **Dextromethorphan** is a multi-target agent whose sigma-1 activity is one of several mechanisms.

Blarcamesine occupies a distinctive position as the sigma-1 receptor agonist with the most advanced and broadest clinical development program across neurodegenerative and neurodevelopmental indications. It is the only compound in this comparator panel with positive Phase 2b/3 data in Alzheimer's disease on a cognitive primary endpoint, the only compound with positive Phase 3 data in Rett syndrome, and the only compound with Phase 2 proof-of-concept data in Parkinson's disease dementia. The dual sigma-1/muscarinic mechanism may confer advantages for cognitive indications relative to more selective sigma-1 agonists such as pridopidine and cutamesine, though the mixed mechanism also introduces complexity in attributing clinical effects to specific receptor targets.

The principal limitation of blarcamesine relative to the comparator panel is the CHMP negative opinion on the Alzheimer's disease application, which raises questions about the strength of the efficacy evidence in the broader patient population (beyond those with specific SIGMAR1 gene variants) and about the tolerability profile as a potential barrier to clinical adoption. Investigators considering blarcame-

sine for research applications should weigh the breadth of the clinical evidence base and the multi-target mechanism against the regulatory uncertainty and the questions about generalizability of the precision medicine approach.

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