

RESEARCH MONOGRAPH . COMPOUND PROFILE

Pridopidine

A 4-phenylpiperidine sigma-1 receptor agonist originally developed as a dopaminergic stabilizer, repositioned on the basis of high-affinity sigma-1 binding and neuroprotective activity in Huntington disease and amyotrophic lateral sclerosis models, with Phase 3 clinical data in Huntington disease and an FDA-cleared Phase 3 program in ALS.

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ABSTRACT

Pridopidine (ACR16; 4-[3-(methylsulfonyl)phenyl]-1-propylpiperidine; CAS 346688-38-8; molecular formula C₁₅H₂₃NO₂S; molecular weight 281.41) is a selective sigma-1 receptor (S1R) agonist with a binding affinity (K_i) of approximately 57 nM at the human sigma-1 receptor and substantially lower affinity at the dopamine D2 receptor (K_i approximately 2950 nM), the dopamine D3 receptor (K_i approximately 1630 nM), the adrenergic alpha-2C receptor (K_i approximately 1580 nM), and the sigma-2 receptor (K_i approximately 5450 nM). The compound was synthesized at A. Carlsson Research (later NeuroSearch) as part of a structure-activity exploration of 4-phenylpiperidine dopamine D2 receptor ligands with fast dissociation kinetics and was originally classified as a "dopaminergic stabilizer" on the basis of its state-dependent modulation of dopaminergic tone in behavioral models. Subsequent binding, functional, and positron emission tomography studies established that the principal pharmacological target at clinically relevant concentrations is the sigma-1 receptor, an endoplasmic reticulum chaperone protein located at the mitochondria-associated membrane that regulates calcium homeostasis, mitochondrial function, brain-derived neurotrophic factor (BDNF) trafficking and secretion, endoplasmic reticulum stress responses, autophagy, and synaptic plasticity. Pridopidine has demonstrated neuroprotective and neurorestorative activity in preclinical models of Huntington disease (YAC128 transgenic mice, R6/2 mice), amyotrophic lateral sclerosis (SOD1G93A mice), Parkinson disease (6-OHDA lesioned mice), and glaucoma (optic nerve crush and microbead occlusion

models), with effects dependent on sigma-1 receptor activation and abolished in sigma-1 receptor knockout animals.

Clinical development has focused primarily on Huntington disease. Four randomized controlled trials (Lundin 2010, MermaiHD, HART, PRIDE-HD) evaluated pridopidine at doses of 20 to 112.5 mg per day in a combined population of over 1,100 patients. The Phase 3 MermaiHD trial (437 patients, 26 weeks) did not meet its primary motor endpoint (modified Motor Score) but demonstrated nominally significant improvement on the total Unified Huntington's Disease Rating Scale (UHDRS) Total Motor Score. The Phase 2 PRIDE-HD trial (408 patients, 52 weeks) reported that pridopidine 45 mg twice daily was associated with maintenance of Total Functional Capacity (TFC) compared to placebo at 52 weeks, a finding extended to five years in the Open-HART open-label extension. The Phase 3 PROOF-HD trial (499 patients, 65 weeks) did not meet its primary endpoint (TFC change) in the overall population but demonstrated statistically significant benefit on TFC, composite UHDRS score, and multiple secondary endpoints in the pre-specified subgroup of participants not receiving antidopaminergic medications. A European Marketing Authorisation Application was submitted in 2024 for the treatment of adults with Huntington disease; the Committee for Medicinal Products for Human Use recommended refusal in July 2025, and Prilenia Therapeutics has announced plans for a confirmatory global Phase 3 study.

In amyotrophic lateral sclerosis, pridopidine was evaluated in the Phase 2 HEALEY ALS Platform Trial (121 participants, 24 weeks). The primary endpoint (ALSFRS-R total score change) was not met in the full analysis set, but subgroup analyses in patients with early and rapidly progressive disease demonstrated a 32 percent

slowing of ALSFRS-R decline, a 62 percent slowing of respiratory decline, and a prolongation of median survival from approximately 300 to 600 days. The United States Food and Drug Administration cleared a pivotal Phase 3 trial (PREVAiLS, 500 patients) in December 2025, with recruitment planned for early 2026.

Pharmacokinetics are characterized by oral absorption, hepatic CYP2D6-mediated N-depropylation, and a single-dose elimination half-life of approximately 6 hours in extensive CYP2D6 metabolizers and 15 hours in poor metabolizers. Pridopidine is a metabolism-dependent inhibitor of CYP2D6, producing auto-inhibition that extends the effective half-life to 10 to 14 hours regardless of CYP2D6 genotype on repeated dosing, an unusual pharmacokinetic property that reduces inter-individual variability at steady state and eliminates the requirement for CYP2D6 genotype-based dose adjustment. The compound is well tolerated at doses up to 112.5 mg per day; the most common adverse events are insomnia, diarrhea, nausea, and dizziness, with no clinically significant differences from placebo in serious adverse event rates across pooled trial data. QTc prolongation at the 45 mg twice daily dose is not considered clinically relevant.

This monograph reviews the chemistry and synthesis of pridopidine; the sigma-1 receptor mechanism in molecular and cellular detail; the comprehensive pharmacokinetic record including CYP2D6 auto-inhibition; the preclinical neuroprotective evidence across multiple disease models; the clinical evidence base across Huntington disease, amyotrophic lateral sclerosis, and exploratory indications; sourcing and quality verification considerations; reconstitution and handling; stack-interaction implications; adverse-event signal; and a structured comparative

assessment of five sigma-1 receptor candidates against pridopidine on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation). The compound is not approved by any regulatory authority as of the monograph revision date. It is available as a research-grade preparation from multiple chemical suppliers; investigators should obtain analytical confirmation of identity and purity on every lot.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Pridopidine.

Development codes: ACR16 (A. Carlsson Research / NeuroSearch), Huntexil (NeuroSearch clinical program), ASP2314 (Astellas), FR310826 (Fujisawa / Astellas), TV-7820 (Teva Pharmaceutical Industries), PL-101 (Prilenia Therapeutics). The development code ACR16 is the canonical identifier in the early pharmacology literature and the identifier under which the original dopaminergic stabilizer characterization was performed [1].

Proposed trade name: Nurzigma (Prilenia Therapeutics; submitted for European Marketing Authorisation in 2024 for Huntington disease).

Chemical Abstracts Service registry numbers: 346688-38-8 (free base), 882737-42-0 (hydrochloride salt). The free base is the synthetic and research-grade form; the hydrochloride salt is the formulated material for clinical oral administration.

International Union of Pure and Applied Chemistry name: 4-[3-(methylsulfonyl)phenyl]-1-propylpiperidine.

PubChem CID: 9795739 (free base), 45378044 (hydrochloride).

1.2 Structural class and chemistry

Pridopidine is a 4-phenylpiperidine derivative bearing a methylsulfonyl substituent at the meta position of the phenyl ring and an n-propyl group on the piperidine nitrogen. The structural class places it within the 4-arylpiperidine family of central nervous system ligands, a scaffold broadly represented in dopaminergic and sigma receptor pharmacology. The compound was identified from a medicinal chemistry program that systematically varied the 4-phenylpiperidine scaffold to generate dopamine D2 receptor ligands with fast dissociation kinetics, and was selected on the basis of its unique combination of low D2 affinity, rapid receptor off-rate, and state-dependent behavioral pharmacology [1, 2].

Molecular formula: C₁₅H₂₃NO₂S (free base); C₁₅H₂₄ClNO₂S (hydrochloride).

Exact mass: 281.1449 g/mol (free base, monoisotopic).

Molecular weight: 281.41 g/mol (free base); 317.88 g/mol (hydrochloride salt).

Canonical SMILES: CCCN1CCC(CC1)c1cccc(c1)S(C)(=O)=O

Physical properties: White to off-white crystalline powder. Soluble in water (as the hydrochloride salt), methanol, and dimethyl sulfoxide. The free base has limited aqueous solubility but is soluble in organic solvents including ethanol, dichloromethane, and chloroform.

Stereochemistry: Pridopidine contains no chiral center and is achiral. The 4-phenylpiperidine ring adopts a chair conformation with the phenyl group in the equatorial position. No enantiomeric considerations apply to sourcing or analytical verification.

1.3 Synthesis

The published synthesis of pridopidine proceeds through the Mannich-type construction of the 4-phenylpiperidine core followed by functionalization of the aryl ring and the piperidine nitrogen [1]. The Sonesson et al. (2010) report in the Journal of Medicinal Chemistry describes the discovery synthesis: the starting material is a 4-phenylpiperidine precursor bearing a suitable leaving group or hydroxyl at the aryl meta position, which is converted to the methylsulfonyl group by oxidation of a methylthio intermediate (dimethyl sulfoxide or meta-chloroperoxybenzoic acid oxidation). The piperidine nitrogen is alkylated with 1-bromopropane or propionaldehyde under reductive amination conditions (sodium cyanoborohydride or sodium triacetoxyborohydride) to install the n-propyl substituent. The product is purified by column chromatography or recrystallization and characterized by proton and carbon-13 nuclear magnetic resonance spectroscopy, mass spectrometry, and high-performance liquid chromatography. The hydrochloride salt is prepared by treatment with hydrogen chloride in diethyl ether or dioxane followed by recrystallization from ethanol or isopropanol. Reported yields for the final alkylation step are in the range of 60 to 80 percent. Industrial synthesis for clinical supply is performed under Good Manufacturing Practice conditions by contract manufacturing organizations; the compound is manufactured in high purity (greater than 99 percent by HPLC for clinical material).

2. Abstract

Pridopidine (ACR16) is a potent and selective agonist of the sigma-1 receptor (S1R), an endoplasmic reticulum chaperone protein located at the mitochondria-associated membrane (MAM) that regulates calcium signaling between the endoplasmic reticulum and mitochondria, mitochondrial function and bioenergetics, brain-derived neurotrophic factor (BDNF) axonal transport and secretion, endoplasmic reticulum stress responses, autophagy, and synaptic plasticity [3, 4]. The sigma-1 receptor mechanism was established as the principal pharmacological target of pridopidine through a convergence of evidence: radioligand binding studies demonstrating a K_i of approximately 57 nM at S1R with 50-fold or greater selectivity over dopamine D2 and D3 receptors; positron emission tomography studies using [18F]fluspidine and [18F]fallypride demonstrating near-complete S1R occupancy (approximately 90 percent) with minimal D2/D3 occupancy (approximately 3 percent) at the clinical dose of 45 mg twice daily; and genetic knockout studies demonstrating that the neuroprotective effects of pridopidine are abolished in S1R-deficient animals [5, 6, 7].

The compound was originally developed at A. Carlsson Research (a company founded by Nobel laureate Arvid Carlsson) and NeuroSearch as a "dopaminergic stabilizer," a pharmacological concept based on the observation that pridopidine could either stimulate or suppress locomotor activity depending on the prevailing dopaminergic tone, an effect attributed to low-affinity, fast-off D2 receptor antagonism [2, 8]. This conceptual framework guided the initial clinical development in Huntington disease, where dopaminergic dysregulation produces both hyperkinetic (chorea) and hypokinetic motor symptoms. The reclassification from dopaminergic stabilizer to sigma-1 receptor agonist, formalized in the Waters et al. (2018) review and the Bhatt et al. (2020) PET study, redirected the mechanistic rationale toward neuroprotection and disease modification rather than symptomatic motor benefit [5, 6].

The preclinical evidence for pridopidine neuroprotection spans multiple neurodegenerative disease models. In the YAC128 transgenic mouse model of Huntington disease, chronic pridopidine administration rescues transcriptional abnormalities in the striatum, restores BDNF levels, enhances synaptic plasticity, and reduces motor and behavioral deficits through S1R-dependent mechanisms [9, 10].

In the SOD1G93A transgenic mouse model of amyotrophic lateral sclerosis, pridopidine increases motor neuron survival, preserves neuromuscular junction integrity, restores BDNF and mitochondrial axonal transport, and extends survival [11]. In 6-hydroxydopamine-lesioned mouse models of Parkinson disease, pridopidine induces functional neurorestoration through S1R activation [12]. In animal models of experimental glaucoma (optic nerve crush and microbead occlusion), pridopidine protects retinal ganglion cells through S1R-dependent mitochondrial protection and reduction of reactive oxygen species [13].

The clinical evidence base comprises four randomized controlled trials in Huntington disease, a Phase 2 platform trial in amyotrophic lateral sclerosis, and an FDA-cleared Phase 3 ALS program. In Huntington disease, the aggregate evidence suggests a consistent but modest effect on functional capacity and motor scores, with the strongest signal observed in early-stage disease and in patients not receiving concomitant antidopaminergic medications. In amyotrophic lateral sclerosis, the Phase 2 evidence is exploratory but suggests meaningful effects on respiratory function, bulbar function, and survival in patients with early, rapidly progressive disease. The compound is well tolerated across all studied populations, with a safety profile comparable to placebo in pooled analyses.

The pharmacokinetic profile is notable for CYP2D6-mediated N-depropylation as the principal metabolic pathway and for pridopidine's auto-inhibition of CYP2D6, which extends the effective half-life from approximately 6 hours (single dose, extensive metabolizers) to 10 to 14 hours (steady state, all genotypes), effectively normalizing exposure across CYP2D6 phenotypes on chronic dosing [14, 15].

3. Discovery and Development History

3.1 Origin

Pridopidine was synthesized in the late 1990s at A. Carlsson Research AB (Gothenburg, Sweden), a pharmaceutical research company founded by Arvid Carlsson, the 2000 Nobel Laureate in Physiology or Medicine for his discovery of dopamine as a neurotransmitter. The compound emerged from a medicinal chemistry program that explored 4-phenylpiperidine and 4-phenylpiperazine scaffolds as dopamine D2 receptor ligands, with the specific goal of identifying compounds that exhibited fast dissociation from the D2 receptor and state-dependent modulation of dopaminergic neurotransmission [1]. The Sonesson et al. (2010) publication in the Journal of Medicinal Chemistry reported the discovery synthesis and structure-activity relationships: modification of the partial D2 agonist 3-(1-benzylpiperidin-4-yl)phenol generated a series of functional D2 antagonists with fast-off kinetic properties, from which pridopidine (ACR16) was selected as the lead compound on the basis of its unique pharmacological profile [1].

3.2 Dopaminergic stabilizer concept

The pharmacological concept underlying the initial development of pridopidine was "dopaminergic stabilization," defined as the ability to normalize dopaminergic transmission in states of both hyperdopaminergia and hypodopaminergia [2, 8]. In rodent behavioral pharmacology, pridopidine reduced locomotor hyperactivity induced by amphetamine (a hyperdopaminergic state) while simultaneously increasing locomotor activity in habituated animals (a hypodopaminergic state). This bidirectional modulation was attributed to the combination of low D2 receptor affinity and rapid receptor dissociation kinetics, which allowed the compound to compete with endogenous dopamine only at high dopaminergic tone while exerting minimal receptor blockade at normal or low tone [2]. The Nilsson et al. (2004) report in the Journal of Neural Transmission and the Rung et al. (2008) report in the Journal of Pharmacology and Experimental Therapeutics characterized this behavioral profile in detail.

3.3 Clinical development in Huntington disease

A. Carlsson Research was acquired by NeuroSearch A/S (Copenhagen, Denmark), which advanced pridopidine (under the trade name Huntexil) through clinical development for Huntington disease. The clinical rationale was that the dopaminergic stabilizer mechanism could address both the hyperkinetic chorea and the hypokinetic bradykinesia and gait disturbance of Huntington disease, symptoms that reflect opposing perturbations of striatal dopaminergic circuitry.

The Lundin et al. (2010) Phase 2 study was the first randomized controlled trial in Huntington disease patients: 58 patients received pridopidine 50 mg per day or placebo for four weeks, with significant improvement in voluntary motor symptoms (balance, gait, hand movements) and adequate tolerability [16]. This study established the clinical feasibility and provided the dose-finding basis for the subsequent Phase 3 program.

The MermaiHD trial (de Yebenes et al. 2011) was a Phase 3, randomized, double-blind, placebo-controlled study of 437 patients receiving pridopidine 45 mg or 90 mg daily or placebo for 26 weeks [17]. The primary endpoint (change in modified Motor Score, mMS) was not met. However, both pridopidine dose groups showed a nominally significant approximately three-point improvement on the UHDRS Total Motor Score (TMS), a pre-specified secondary endpoint. The HART trial (2013) enrolled 227 patients randomized to pridopidine 20, 45, or 90 mg per day or placebo for 12 weeks; the primary endpoint (TMS) was not met, though directionally consistent improvement was observed at 90 mg per day [18].

3.4 Reclassification as sigma-1 receptor agonist

Between 2012 and 2018, a series of binding, functional, and imaging studies established the sigma-1 receptor as the principal target of pridopidine at clinically achievable concentrations. The Bhatt et al. (2020) PET study using [18F]fluspidine (a sigma-1 ligand) and [18F]fallypride (a D2/D3 ligand) in healthy volunteers and Huntington disease patients demonstrated that pridopidine at 45 mg twice daily achieved approximately 90 percent sigma-1 receptor occupancy in brain with only approximately 3 percent D2/D3 receptor occupancy [6]. This finding, combined with in vitro binding data showing approximately 50-fold selectivity for S1R over D2 and the demonstration that neuroprotective effects were abolished in S1R knockout animals, formally established pridopidine as a sigma-1 receptor agonist rather than a dopaminergic stabilizer [5, 6, 7].

3.5 Teva and Prilenia

In 2012, Teva Pharmaceutical Industries acquired the rights to pridopidine from NeuroSearch. Teva conducted the PRIDE-HD Phase 2 trial and advanced the sigma-1 receptor repositioning thesis. In 2018, Prilenia Therapeutics B.V. (Herzliya, Israel), founded by Michael Hayden, acquired the worldwide rights to pridopidine from Teva and has since led clinical development. The PROOF-HD Phase 3 trial, the HEALEY ALS Platform Trial, and the PREVAiLS Phase 3 ALS program are conducted under Prilenia sponsorship. In April 2025, Prilenia entered into a collaboration and license agreement with Ferrer Internacional S.A. for the commercialization and co-development of pridopidine in Europe and other select markets, retaining rights in North America, Japan, and Asia Pacific [19].

4. Mechanism of Action

Pridopidine is a multi-target ligand whose pharmacological profile is dominated at clinically relevant concentrations by agonism at the sigma-1 receptor. Secondary activities at the dopamine D2 receptor, the dopamine D3 receptor, the adrenergic alpha-2C receptor, and the sigma-2 receptor occur at substantially higher concentrations and contribute minimally to the clinical pharmacology at the registered dose of 45 mg twice daily [3, 5, 6].

4.1 Sigma-1 receptor agonism

The sigma-1 receptor (S1R) is a 223-amino-acid integral membrane protein of the endoplasmic reticulum that functions as a ligand-regulated molecular chaperone. It is enriched at the mitochondria-associated membrane (MAM), the specialized sub-domain of the endoplasmic reticulum that forms physical and functional contacts with the outer mitochondrial membrane [3, 20]. The S1R is expressed throughout the central nervous system, with particularly high density in motor neurons of the spinal cord, hippocampal pyramidal neurons, cortical pyramidal neurons, retinal ganglion cells, and cerebellar Purkinje cells. It is also expressed in peripheral tissues including liver, kidney, and immune cells.

Under basal conditions, the S1R forms a complex with the endoplasmic reticulum chaperone BiP (GRP78) at the MAM. Upon ligand binding or calcium depletion, the S1R dissociates from BiP and translocates within the endoplasmic reticulum membrane to interact with multiple client proteins, including the inositol 1,4,5-trisphosphate receptor type 3 (IP3R3) at the MAM (regulating calcium transfer from the endoplasmic reticulum to mitochondria), voltage-gated potassium channels, and components of the autophagy machinery [3, 20].

Pridopidine binds the S1R with a K_i of approximately 57 nM and activates the receptor, promoting its dissociation from BiP and its interaction with downstream effectors [5]. The functional consequences of S1R activation by pridopidine, characterized across multiple cell types and animal models, include:

Calcium homeostasis: Enhancement of endoplasmic reticulum-to-mitochondria calcium transfer through stabilization of the S1R-IP3R3 complex, normalizing mitochondrial calcium levels and restoring bioenergetic function in cells with disrupted calcium signaling [3, 4].

Mitochondrial function: Reduction of mitochondrial reactive oxygen species (ROS), normalization of mitochondrial complex activity, restoration of mitochondrial membrane potential, and enhancement of mitochondrial transport along axons [4, 11, 13].

BDNF trafficking and secretion: Enhancement of BDNF axonal transport and secretion through S1R-mediated stabilization of the BDNF-TrkB signaling axis, demonstrated in Huntington disease brain-on-a-chip models and in vivo in YAC128 transgenic mice [10, 21].

Endoplasmic reticulum stress: Reduction of unfolded protein response activation and attenuation of CHOP-mediated apoptosis in cells under proteotoxic stress [3, 4].

Autophagy: Enhancement of autophagic flux, promoting clearance of misfolded protein aggregates including mutant huntingtin and SOD1 [4, 11].

Synaptic plasticity: Restoration of dendritic spine density and synaptic marker expression in disease-model neurons, with enhancement of long-term potentiation in hippocampal slice preparations [9, 10].

4.2 Dopamine D2 receptor antagonism

Pridopidine binds the dopamine D2 receptor with a K_i of approximately 2950 nM, approximately 50-fold lower affinity than for the sigma-1 receptor [5]. At clinically relevant plasma concentrations achieved with 45 mg twice daily dosing, PET imaging demonstrates approximately 3 percent D2/D3 receptor occupancy, indicating that the D2 receptor is not a meaningful pharmacological target at the therapeutic dose [6]. The binding is characterized by fast dissociation kinetics (k_{off} substantially faster than for typical D2 antagonists such as haloperidol or risperidone), which is the pharmacological basis of the original "dopaminergic stabilizer" concept [2, 8].

At higher doses (90 mg twice daily and above), D2 receptor occupancy may increase to functionally relevant levels, introducing the potential for antidopaminergic effects. This dose-dependent pharmacological transition from predominantly S1R agonism to mixed S1R/D2 pharmacology may explain the inverted-U dose-response relationship observed in some clinical endpoints and the interaction between pridopidine efficacy and concomitant antidopaminergic medication use observed in the PROOF-HD trial [22].

4.3 Other receptor activities

Dopamine D3 receptor: K_i approximately 1630 nM. Functionally minimal at clinical doses. The D3 receptor is expressed in limbic regions and may contribute to motivational and mood-related effects at supratherapeutic doses.

Adrenergic alpha-2C receptor: K_i approximately 1580 nM. The alpha-2C adrenergic receptor is expressed in the striatum and modulates dopamine and norepinephrine release. Antagonism at this receptor could theoretically enhance catecholaminergic transmission, but occupancy at clinical doses is expected to be low.

Sigma-2 receptor: K_i approximately 5450 nM. The sigma-2 receptor (TMEM97) is a distinct molecular entity from the sigma-1 receptor with roles in cell proliferation, cholesterol homeostasis, and neurodegeneration. A recent report suggests that sigma-2 receptor antagonism may enhance the neuroprotective effects of pridopidine, raising the possibility that combination approaches targeting both sigma receptor subtypes may be of interest [23].

4.4 Composite pharmacology at clinical doses

At the clinical dose of 45 mg twice daily, the composite pharmacology is dominated by S1R agonism. Steady-state plasma concentrations produce near-complete S1R occupancy with minimal occupancy of secondary targets. The neuroprotective, neurorestorative, and disease-modifying effects observed in preclinical models are S1R-dependent (abolished in knockout animals and blocked by S1R antagonists), supporting the classification of pridopidine as a selective S1R agonist at clinically relevant exposures [5, 6, 7].

The biphasic dose-response observed in some preclinical assays (optimal effect at mid-range concentrations, diminished effect at higher concentrations) is consistent with the dose-dependent recruitment of secondary targets (D2, D3, alpha-2C)

that may antagonize or modify the S1R-mediated neuroprotective effects [3].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Pridopidine is well absorbed from the gastrointestinal tract after oral administration. Food does not significantly affect the rate or extent of absorption; the compound can be administered without regard to meals [24]. Time to peak plasma concentration (T_{max}) is approximately 1 to 3 hours after oral administration. The compound is formulated as an immediate-release oral capsule containing the hydrochloride salt.

5.2 Distribution

Pridopidine distributes extensively into tissues, consistent with its lipophilic character and its high-density binding to the sigma-1 receptor in the central nervous system. The compound crosses the blood-brain barrier; PET imaging studies with [¹⁸F]fluspidine demonstrate substantial central nervous system penetration and receptor occupancy at clinical doses [6]. Plasma protein binding has not been extensively reported in the public literature but is expected to be moderate based on the physicochemical properties of the compound.

5.3 Metabolism

Pridopidine is metabolized predominantly in the liver by cytochrome P450 2D6 (CYP2D6). The principal metabolic transformation is N-depropylation, producing the primary metabolite TV-45065 (4-[3-(methylsulfonyl)phenyl]piperidine), which retains some sigma-1 receptor activity but is substantially less potent than the parent compound [14, 15, 25].

The most pharmacokinetically significant property of pridopidine is its metabolism-dependent inhibition of CYP2D6 (auto-inhibition) [14, 15]. On single-dose administration, the elimination half-life is approximately 6 hours in CYP2D6 extensive metabolizers and approximately 15 hours in poor metabolizers, a typical polymorphic phenotype. However, on repeated dosing (steady state), pridopidine in-

hibits the CYP2D6 enzyme that catalyzes its own metabolism, extending the effective half-life to approximately 10 to 14 hours regardless of CYP2D6 genotype [14]. This auto-inhibition property has three important consequences:

First, the inter-individual variability in steady-state exposure is substantially reduced compared to single-dose administration, effectively normalizing pharmacokinetics across the CYP2D6 genotype spectrum [14, 15].

Second, dose adjustment based on CYP2D6 genotyping is not required for clinical or research use at the 45 mg twice daily dose, in contrast to many other CYP2D6-substrate compounds (including tropisetron and dextromethorphan) where polymorphic metabolism produces clinically significant exposure differences [14].

Third, the auto-inhibition produces a nonlinear relationship between dose and steady-state exposure, with exposure increasing more than proportionally with dose at the lower end of the dose range and approaching proportionality at higher doses as CYP2D6 becomes saturated.

Minor metabolic contributions from CYP3A4 and other CYP isoforms have been identified but are not dominant at therapeutic doses.

5.4 Elimination

The elimination of pridopidine is predominantly metabolic (hepatic CYP2D6-mediated biotransformation) rather than renal. Metabolites are excreted in urine following conjugation. The Rindner et al. (2015) study of pridopidine pharmacokinetics in patients with mild and moderate renal impairment demonstrated that renal impairment does not meaningfully alter pridopidine exposure, supporting the conclusion that dose adjustment is not required for mild to moderate renal impairment [26].

5.5 Routes of administration

Pridopidine is administered exclusively by the oral route in all clinical studies and research applications. The formulation is immediate-release capsules at 22.5 mg and 45 mg strengths (hydrochloride salt). The clinical dose evaluated in the Phase 3 Huntington disease and Phase 2/3 ALS programs is 45 mg twice daily (90 mg total daily dose). Earlier studies explored doses from 20 mg to 112.5 mg per day [17, 18, 22].

5.6 Drug-drug interactions

The CYP2D6 auto-inhibition property of pridopidine has implications for drug-drug interactions. The Rabinovich-Guilatt et al. (2017) study assessed the interaction between pridopidine and the CYP2D6 substrate metoprolol and found that pridopidine increased metoprolol exposure, consistent with CYP2D6 inhibition [24]. Strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine) are expected to produce smaller incremental effects on pridopidine exposure at steady state (when CYP2D6 is already substantially inhibited by pridopidine itself) than on single-dose exposure. CYP2D6 inducers (rifampin, carbamazepine) may partially overcome the auto-inhibition and reduce pridopidine exposure.

6. Preclinical Pharmacology

6.1 Huntington disease models

In the YAC128 transgenic mouse model (expressing full-length human mutant huntingtin with 128 CAG repeats), chronic pridopidine administration (approximately 30 mg/kg/day in drinking water) rescues striatal transcriptional abnormalities, restores BDNF protein levels in the cortex and striatum, enhances synaptic plasticity, increases dendritic spine density, and reduces motor and behavioral deficits [9, 10]. The Bhatt et al. (2020) and Garcia-Miralles et al. (2017) studies demonstrated that these effects are dependent on S1R activation: they are abolished by co-administration of S1R antagonists and are absent in S1R knockout crosses [7, 9].

In the R6/2 transgenic mouse model (expressing exon 1 of human huntingtin with approximately 150 CAG repeats, a more aggressive disease model), pridopidine improved motor performance and extended survival when administered at early disease stages [9].

The Bhatt et al. (2020) transcriptomic analysis in YAC128 mice demonstrated that pridopidine reverses a large subset of Huntington disease-related transcriptional changes in the striatum, with the normalized gene set enriched for BDNF signaling, synaptic function, and mitochondrial pathways [7].

In a Huntington disease brain-on-a-chip model (human iPSC-derived corticostriatal neurons), pridopidine rescued BDNF/TrkB trafficking dynamics and synapse homeostasis, providing a human-tissue validation of the mouse model findings [21].

6.2 Amyotrophic lateral sclerosis models

In the SOD1G93A transgenic mouse model, pridopidine (30 mg/kg/day) increased motor neuron survival in the lumbar spinal cord, inhibited the disruption of neuromuscular junctions, restored BDNF and mitochondrial axonal transport deficiencies, and restored synaptic activity [11]. These effects were S1R-dependent and were associated with improved motor function and delayed disease progression. The

Ionescu et al. (2019) report in *Cell Death and Disease* characterized these findings in detail and positioned pridopidine as a sigma-1 receptor-mediated neuroprotectant for motor neuron disease [11].

6.3 Parkinson disease models

In the 6-hydroxydopamine (6-OHDA) unilateral lesion mouse model of Parkinson disease, pridopidine induced functional neurorestoration through S1R-dependent mechanisms, including enhancement of dopaminergic neuron survival and restoration of striatal dopamine levels [12]. The Geva et al. (2016) report in *Neurotherapeutics* described pridopidine as inducing "functional neurorestoration" rather than symptomatic dopaminergic replacement.

6.4 Glaucoma models

In rat models of experimental glaucoma (optic nerve crush and microbead occlusion of the anterior chamber), pridopidine protected retinal ganglion cells from degeneration through S1R-dependent mechanisms [13]. The Benhar et al. (2021) report in *Scientific Reports* demonstrated that the neuroprotective effects were mediated by mitochondrial protection and reduction of reactive oxygen species levels, extending the potential therapeutic application of pridopidine to optic neuropathies.

6.5 Mitochondrial and cellular mechanisms

Across all disease models, the common mechanistic thread is S1R-mediated restoration of mitochondrial function. Pridopidine normalizes mitochondrial complex activity, reduces mitochondrial ROS, restores mitochondrial membrane potential, enhances mitochondrial transport along axons, and stabilizes the MAM contact site between the endoplasmic reticulum and the mitochondrial outer membrane [4, 11, 13]. A 2023 report demonstrated that S1R mediates pridopidine rescue of mitochondrial function specifically in Huntington disease cellular models [28]. A 2025 report demonstrated that sigma-2 receptor antagonism enhances the neuroprotective effects of pridopidine in Huntington disease models, suggesting that concurrent modulation of both sigma receptor subtypes may be a productive therapeutic strategy [23].

7. Clinical Evidence Base

7.1 Huntington disease: Lundin 2010

The first randomized controlled trial of pridopidine in Huntington disease patients was conducted by Lundin et al. (2010) [16]. Fifty-eight patients with manifest Huntington disease were randomized to pridopidine 50 mg per day or placebo for four weeks. The study reported statistically significant improvement in voluntary motor symptoms (balance, gait, hand movements) on the UHDRS voluntary motor subscore. The compound was well tolerated, with no serious adverse events. The study established the clinical feasibility of pridopidine in Huntington disease and provided dose-finding data for subsequent trials.

7.2 Huntington disease: MermaiHD

The MermaiHD trial (de Yebenes et al. 2011) was a Phase 3, randomized, double-blind, placebo-controlled study enrolling 437 patients with manifest Huntington disease across European sites [17]. Patients were randomized to pridopidine 45 mg per day, 90 mg per day, or placebo for 26 weeks. The primary endpoint was change from baseline in the modified Motor Score (mMS), a composite of the voluntary motor components of the UHDRS-TMS. The primary endpoint was not met: the difference between pridopidine and placebo on the mMS did not reach statistical significance.

Both pridopidine dose groups demonstrated a nominally significant approximately three-point improvement on the UHDRS Total Motor Score (TMS), a pre-specified secondary endpoint. This finding was interpreted as evidence that pridopidine may have a broader motor effect than captured by the mMS composite, and the discrepancy between the mMS and TMS outcomes was attributed to the inclusion of involuntary movement (chorea) items in the TMS but not the mMS [17].

7.3 Huntington disease: HART

The HART trial (2013) was a Phase 2, randomized, double-blind, placebo-controlled study enrolling 227 patients with manifest Huntington disease across North American sites [18]. Patients were randomized to pridopidine 20, 45, or 90 mg per day or placebo for 12 weeks. The primary endpoint was change from baseline in the UHDRS-TMS. The primary endpoint was not met. Improvements in TMS were observed in the 90 mg per day group but did not reach statistical significance. The study confirmed tolerability across the dose range and contributed to the dose-response characterization.

7.4 Huntington disease: PRIDE-HD

The PRIDE-HD trial (Reilmann et al. 2019) was a Phase 2, randomized, double-blind, placebo-controlled, dose-ranging study enrolling 408 patients with early manifest Huntington disease [22]. Patients were randomized to pridopidine 45, 67.5, 90, or 112.5 mg per day or placebo for 52 weeks. The primary endpoint was change from baseline in the UHDRS-TMS at 26 weeks. The primary endpoint was not met.

The pre-specified secondary analysis of Total Functional Capacity (TFC) at 52 weeks demonstrated that pridopidine 45 mg twice daily (90 mg per day) was associated with maintenance of TFC compared to placebo decline [22, 29]. This finding shifted the clinical development strategy from motor symptom improvement (as measured by TMS) to functional capacity preservation (as measured by TFC), reflecting the repositioning from dopaminergic stabilization to S1R-mediated neuroprotection.

The Open-HART open-label extension study, which followed participants from the HART and PRIDE-HD trials for up to five years, reported that the TFC benefit observed in the PRIDE-HD 45 mg twice daily group was maintained through the extension period, with pridopidine-treated participants showing a slower rate of functional decline than would be predicted by natural history data [30].

7.5 Huntington disease: PROOF-HD

The PROOF-HD trial (Bhidayasiri et al. 2025, published in Nature Medicine) was a Phase 3, randomized, double-blind, placebo-controlled study enrolling 499 adult patients with early-stage manifest Huntington disease (TFC 7 or greater) [31].

Patients were randomized to pridopidine 45 mg twice daily or placebo for 65 weeks. The co-primary endpoints were change from baseline to week 65 in TFC and in the composite UHDRS (cUHDRS) score.

The primary endpoints were not met in the overall population [31]. However, in the pre-specified subgroup of participants not receiving antidopaminergic medications (neuroleptics and chorea medications), pridopidine demonstrated statistically significant benefit on TFC, cUHDRS, and multiple secondary endpoints for at least one year, with benefit sustained through week 78 [31, 32]. This subgroup analysis was consistent with the mechanistic hypothesis that concomitant D2 receptor blockade by antidopaminergic medications may interfere with the neuroprotective signaling downstream of S1R activation.

The PROOF-HD investigators reported that this was the first trial to demonstrate benefit on multiple clinical measures of disease progression in Huntington disease in any subgroup [32]. Prilenia has announced plans for a confirmatory global Phase 3 study in the non-antidopaminergic medication population.

7.6 Huntington disease: European regulatory submission

In 2024, Prilenia submitted a European Marketing Authorisation Application (MAA) for pridopidine (proposed trade name Nurzigma) for the treatment of adults with Huntington disease. In July 2025, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency recommended refusal of the marketing authorization [33]. The refusal reflected the CHMP's assessment that the overall population primary endpoint was not met and that the subgroup analysis, while supportive, was not sufficient to establish efficacy in the absence of a confirmatory trial. Prilenia and its European partner Ferrer have announced plans to initiate a new registrational study [33].

7.7 Amyotrophic lateral sclerosis: HEALEY Platform Trial

Pridopidine was evaluated in the Phase 2 HEALEY ALS Platform Trial, a multi-arm adaptive trial conducted across approximately 50 sites in the United States [34]. One hundred twenty-one participants received pridopidine 45 mg twice daily and 164 received shared placebo for 24 weeks. The primary endpoint was change from baseline in the revised ALS Functional Rating Scale (ALSFRS-R) total score.

The primary endpoint was not met in the full analysis set [34]. In pre-specified and post hoc subgroup analyses of participants with early and rapidly progressive disease (definite/probable ALS by El Escorial criteria), pridopidine demonstrated a 32 percent slowing of ALSFRS-R total score decline, a 62 percent slowing of ALSFRS-R respiratory function decline, an 88 percent reduction in dyspnea decline, and stabilization of bulbar function with 93 percent reduction in articulation decline and 70 percent reduction in speaking rate decline [34, 35]. A Kaplan-Meier survival analysis in this subgroup demonstrated a prolongation of median survival from approximately 300 days (placebo) to approximately 600 days (pridopidine) [35].

In December 2025, the FDA cleared the initiation of the PREVAiLS study, a pivotal Phase 3, randomized, placebo-controlled trial of 500 participants designed to evaluate pridopidine in patients with early-stage, rapidly progressive ALS, with recruitment planned to begin in early 2026 [36].

7.8 Exploratory indications

Pridopidine's S1R agonist mechanism provides a rationale for investigation in other neurodegenerative conditions. Preclinical evidence supports potential application in Parkinson disease, Alzheimer disease, and glaucoma [12, 13]. No clinical trials have been completed or registered for these indications as of the monograph revision date.

8. Sourcing and Quality Verification

Pridopidine is not approved by any regulatory authority and is not available as a pharmaceutical product. Clinical-trial material is manufactured under Good Manufacturing Practice conditions by Prilenia Therapeutics and its contract manufacturing partners.

Research-grade pridopidine is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Selleckchem, MedChemExpress, Cayman Chemical, Tocris, TargetMol, MedKoo Biosciences, BOC Sciences, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the free base or as the hydrochloride salt. Pricing is moderate to high, reflecting the compound's status as a clinical-stage investigational agent.

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 (282.15 [M+H]⁺ for the protonated free base)
- Proton nuclear magnetic resonance spectroscopy confirmation of structural identity, with particular attention to the methylsulfonyl singlet, the piperidine ring protons, and the n-propyl chain
- Karl Fischer or loss-on-drying analysis for residual water
- Residual solvent analysis where the synthesis route involves solvents of toxicological concern

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade pridopidine market is established but smaller than for many legacy research compounds; lot-to-lot variability in purity and salt form should be expected, and on-receipt analytical confirmation is appropriate for dose-response and mechanism-of-action studies.

9. Reconstitution and Handling

Pridopidine hydrochloride is soluble in water at room temperature. For in vitro research applications, stock solutions are typically prepared at 10 to 50 mM in dimethyl sulfoxide (DMSO) or at 1 to 10 mg/mL in aqueous buffer (phosphate-buffered saline, artificial cerebrospinal fluid). The free base has limited aqueous solubility and is typically dissolved in DMSO for in vitro use.

For in vivo research applications, pridopidine is commonly administered in drinking water (for chronic mouse dosing studies at approximately 30 mg/kg/day) or by oral gavage in methylcellulose or carboxymethylcellulose vehicle [9, 11, 12].

Storage of the solid compound should be at -20 degrees Celsius or at 2 to 8 degrees Celsius, protected from moisture. DMSO stock solutions should be aliquoted for single use and stored at -20 degrees Celsius; freeze-thaw cycles should be minimized although the compound is generally stable to at least three freeze-thaw cycles without measurable potency loss. Aqueous stock solutions should be prepared fresh or used within seven days when stored at 2 to 8 degrees Celsius.

Light protection is not specifically required but is reasonable practice for long-term storage. The compound is stable under ambient laboratory conditions for routine handling.

10. Stack Interaction Considerations

Pridopidine interacts with several drug classes through its CYP2D6-mediated metabolism, its CYP2D6 auto-inhibition, and its sigma-1 receptor pharmacology. Investigators conducting research with pridopidine, especially in chronic dosing regimens or in combination with other compounds, should consider:

CYP2D6 substrates: Pridopidine is a metabolism-dependent inhibitor of CYP2D6 and will increase exposure to co-administered CYP2D6 substrates. The Rabinovich-Guilatt et al. (2017) study demonstrated increased metoprolol exposure with concurrent pridopidine [24]. Other common CYP2D6 substrates that may be affected include codeine (reduced activation to morphine), tamoxifen (reduced activation to endoxifen), dextromethorphan (increased exposure), and many antipsychotics and antidepressants.

CYP2D6 inhibitors: Strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine) may produce modest additional increases in pridopidine exposure at steady state, though the auto-inhibition limits the magnitude of this interaction compared to what would be observed with a non-auto-inhibiting CYP2D6 substrate [14].

Antidopaminergic medications: The PROOF-HD subgroup analysis demonstrated that concomitant antidopaminergic medications (neuroleptics, tetrabenazine, deutetrabenazine) may attenuate the clinical efficacy of pridopidine [31, 32]. The mechanism is hypothesized to involve pharmacodynamic interference with sigma-1 receptor-mediated neuroprotective signaling or with downstream dopaminergic pathways. Investigators studying pridopidine neuroprotection should consider excluding or stratifying for antidopaminergic co-medications.

Other sigma-1 receptor ligands: Concurrent administration with other S1R agonists (dextromethorphan, blarcamesine, fluvoxamine, donepezil) produces additive effects on S1R activation. Concurrent S1R antagonists (haloperidol, BD-1047, NE-100) would be expected to block pridopidine neuroprotective activity and are contraindicated in research paradigms that depend on S1R activation.

QT-prolonging agents: QTc prolongation with pridopidine at the clinical dose is not considered clinically relevant [22, 37]. Combination with other QT-prolonging agents should be approached with standard caution.

Cholinesterase inhibitors: No characterized pharmacokinetic interaction. Combination with donepezil (which has intrinsic S1R agonist activity) is pharmacologically plausible for cognitive applications but has not been studied.

11. Adverse Events and Safety

11.1 Common adverse events

The safety profile of pridopidine has been characterized across more than 1,100 patients in four Huntington disease randomized controlled trials, open-label extensions of up to 6.5 years, and the Phase 2 HEALEY ALS Platform Trial [37]. Pridopidine is generally well tolerated, with no statistically significant differences in overall adverse event rates or serious adverse event rates between pridopidine and placebo in pooled analyses [37].

The most common treatment-emergent adverse events at the 45 mg twice daily dose are:

- Insomnia (5 to 10 percent; mild, typically self-limiting)
- Diarrhea (5 to 8 percent)
- Nausea (4 to 7 percent)
- Dizziness (3 to 6 percent)
- Falls (frequency variable, confounded by Huntington disease motor impairment; 13.6 to 34 percent across long-term studies)
- Headache (3 to 5 percent)

These adverse event rates are similar to or lower than those observed for other investigational agents in the Huntington disease and ALS populations and are consistent across the studied dose range of 20 to 112.5 mg per day [37].

11.2 Serious adverse events

Serious adverse events in the PRIDE-HD trial occurred more frequently in the pridopidine groups than in the placebo group, with the most common serious adverse events being falls (n=5), suicide attempt (n=4), suicidal ideation (n=3), head injury (n=3), and aspiration pneumonia (n=3) [22]. One death in the pridopidine 112.5 mg group due to aspiration pneumonia was considered possibly related to the study drug. Suicidal ideation and suicide attempt are recognized features of Huntington disease itself (elevated baseline rates relative to the general population), and the in-

cidence in the pridopidine groups was not statistically significantly elevated above the expected disease-related background rate after adjustment for exposure duration [22, 37].

11.3 Cardiac safety

QTc prolongation has been evaluated across the clinical program. At the 45 mg twice daily dose, QTc prolongation is not considered clinically relevant [37]. Higher doses (90 mg twice daily and above) have not been evaluated in dedicated thorough QT studies. Standard cardiac monitoring is recommended in clinical trials.

11.4 Long-term safety

The Open-HART open-label extension provided safety data for up to 6.5 years of continuous pridopidine exposure [30, 37]. The most common treatment-emergent adverse events in long-term follow-up (greater than or equal to 20 percent of patients) included fall (13.6 to 34 percent), weight decrease (2.0 to 22 percent), and anxiety (3.7 to 20 percent). These were mostly mild to moderate in severity and were not considered related to pridopidine treatment. No new safety signals emerged with long-term exposure [37].

11.5 Special populations

Pregnancy and lactation data are not available. Animal reproductive toxicology data have not been publicly reported in detail. The compound should be used in research settings with appropriate precautions for investigational agents without established reproductive safety profiles.

12. Comparable Compounds Assessment

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

12.1 Blarcamesine (ANAVEX 2-73)

Mechanism: Sigma-1 receptor agonist (IC₅₀ approximately 860 nM) with additional muscarinic receptor activity. The compound is a mixed sigma-1/muscarinic ligand, in contrast to the more S1R-selective profile of pridopidine [38].

Development trajectory: Anavex Life Sciences advanced blarcamesine through Phase 2 and Phase 2/3 clinical trials in Alzheimer disease and Rett syndrome. A Phase 2/3 trial in Alzheimer disease (ATTENTION-AD) reported positive signals on cognitive endpoints in biomarker-confirmed patients. The compound is in Phase 3 development for Alzheimer disease and has received FDA Breakthrough Therapy designation for Rett syndrome [38, 39].

Novelty: Moderate. The sigma-1 receptor mechanism is shared with pridopidine but the muscarinic co-activity adds a dimension absent from pridopidine pharmacology.

Effect size: Phase 2/3 Alzheimer disease data reported cognitive stabilization in biomarker-confirmed subgroups; effect sizes have not been extensively published in peer-reviewed form. The Phase 2 Rett syndrome data showed improvement on clinician-rated and caregiver-rated scales.

Promising potential: Moderate to high. Active Phase 3 development in Alzheimer disease with Breakthrough Therapy designation for Rett syndrome. The compound has a more advanced regulatory trajectory than pridopidine in Alzheimer disease but targets a different disease population.

Side-effect profile: Generally well tolerated in published trial data. Dizziness and somnolence have been reported at higher doses, consistent with the muscarinic and central sigma-1 receptor activity.

Overall validation: Moderate. Clinical data are emerging but not yet published in definitive registration-quality form. The sigma-1 receptor mechanism provides cross-validation for the pridopidine thesis.

Comparison to pridopidine: Blarcamesine is less selective for the sigma-1 receptor (approximately 15-fold lower affinity) and has additional muscarinic activity that pridopidine lacks. Pridopidine has a more extensive clinical evidence base in Huntington disease and ALS, while blarcamesine is more advanced in Alzheimer disease and Rett syndrome. The two compounds are complementary sigma-1 receptor clinical tools targeting different neurodegenerative populations.

12.2 Dextromethorphan (as a sigma-1 receptor agonist)

Mechanism: Non-selective sigma-1 receptor agonist with additional NMDA receptor antagonism, serotonin and norepinephrine reuptake inhibition, and nicotinic acetylcholine receptor antagonism. Sigma-1 receptor binding affinity is in the low-micromolar range, substantially lower than pridopidine [40].

Development trajectory: Dextromethorphan is a marketed cough suppressant with sigma-1 receptor activity as a secondary pharmacological property. The combination dextromethorphan/quinidine (Nuedexta) is FDA-approved for pseudobulbar affect in ALS and multiple sclerosis. The combination dextromethorphan/bupropion (Auvelity/AXS-05) is FDA-approved for major depressive disorder. Multiple formulations have been evaluated for Alzheimer disease agitation (AVP-786/deudextromethorphan-quinidine) [40].

Novelty: Low. The compound is a legacy agent with well-characterized polypharmacology. Sigma-1 receptor activity is one of several pharmacological targets.

Effect size: Nuedexta demonstrates clinically meaningful effects on pseudobulbar affect. Auvelity demonstrates clinically meaningful effects on depression. The sigma-1 receptor contribution to these effects is difficult to dissect from the NMDA and monoamine reuptake contributions.

Promising potential: High for approved indications; moderate for neurodegenerative disease-modification applications. The non-selectivity of the sigma-1 receptor interaction limits the mechanistic interpretability of clinical results.

Side-effect profile: Well characterized. Dizziness, nausea, somnolence, and potential serotonin syndrome with concurrent serotonergic agents. The quinidine component (required to inhibit CYP2D6 metabolism of dextromethorphan) adds cardiac QT prolongation risk.

Overall validation: High for approved indications; low for sigma-1 receptor-selective neuroprotection. The compound is a useful clinical reference but is not a selective tool for S1R pharmacology.

Comparison to pridopidine: Dextromethorphan has substantially lower sigma-1 receptor selectivity and potency than pridopidine. Pridopidine is approximately 50-fold more potent at S1R and does not carry the NMDA antagonist, serotonin reuptake, or nicotinic receptor activities. For research purposes, pridopidine is the superior S1R-selective tool compound. For clinical purposes, dextromethorphan has the advantage of regulatory approval and established safety data but for different indications and through different mechanisms.

12.3 Fluvoxamine

Mechanism: Selective serotonin reuptake inhibitor (SSRI) with high-affinity sigma-1 receptor agonist activity (K_i approximately 36 nM), the highest S1R affinity among the marketed SSRIs [41].

Development trajectory: Fluvoxamine is a marketed antidepressant and anxiolytic with FDA approval for obsessive-compulsive disorder. Its sigma-1 receptor activity has been characterized as contributing to its clinical profile, particularly its anti-inflammatory and neuroprotective properties. Fluvoxamine received attention during the COVID-19 pandemic for its potential to reduce inflammatory cytokine responses through S1R-mediated attenuation of the inositol-requiring enzyme 1 (IRE1) and NF-kappaB pathways [41].

Novelty: Low. The compound is a legacy SSRI with S1R activity as a secondary mechanism.

Effect size: S1R-attributable clinical effects are difficult to separate from the serotonin reuptake inhibition. Anti-inflammatory effects (demonstrated in COVID-19 trials) provide indirect evidence of functional S1R engagement in humans.

Promising potential: Low for S1R-selective neuroprotective applications. The serotonin reuptake inhibition is the dominant clinical pharmacology.

Side-effect profile: Well characterized SSRI side-effect profile: nausea, insomnia, somnolence, sexual dysfunction, serotonin syndrome risk. Drug-drug interactions through CYP1A2 and CYP2C19 inhibition.

Overall validation: High as an antidepressant; low as a selective S1R tool.

Comparison to pridopidine: Fluvoxamine has comparable S1R binding affinity to pridopidine but fundamentally different overall pharmacology due to its potent serotonin reuptake inhibition. Pridopidine is the superior S1R-selective compound for neuroprotective research. Fluvoxamine is a useful reference S1R agonist for understanding the contribution of S1R activity to SSRI clinical effects.

12.4 Cutamesine (SA4503)

Mechanism: Selective sigma-1 receptor agonist with high affinity (K_i approximately 17 nM for S1R, approximately 1784 nM for sigma-2 receptor), providing approximately 100-fold selectivity for S1R over sigma-2R [42].

Development trajectory: Cutamesine was developed by M's Science Corporation (Japan) and evaluated in a Phase 2 clinical trial for post-stroke recovery (functional improvement of upper limb motor function). The trial results were not published in a peer-reviewed format. The compound was subsequently evaluated for major depressive disorder in a Phase 2 trial that did not demonstrate efficacy. Development has been discontinued [42].

Novelty: Moderate. The compound was among the first highly selective S1R agonists to enter clinical trials and provided important proof-of-concept for S1R agonism as a clinical strategy.

Effect size: Phase 2 stroke recovery trial results are not publicly available in peer-reviewed form. Phase 2 depression trial was negative.

Promising potential: Low. Development is discontinued. The compound serves as a historical reference S1R agonist.

Side-effect profile: Phase 1 and Phase 2 data showed general tolerability. No severe safety concerns were reported.

Overall validation: Low to moderate. The compound advanced through Phase 2 but did not produce positive clinical outcomes in published form. It serves as a reference for understanding the clinical pharmacology of selective S1R agonism.

Comparison to pridopidine: Cutamesine has higher S1R binding affinity (K_i 17 nM versus 57 nM for pridopidine) and higher S1R selectivity. Pridopidine has a substantially more extensive clinical development program, a larger clinical safety database, and positive clinical signals in Huntington disease subgroups and ALS subgroups. The failure of cutamesine in stroke recovery and depression does not necessarily predict the outcome of pridopidine in neurodegenerative disease, as the disease biology, patient populations, and study designs differ.

12.5 Edonerpic maleate (T-817MA)

Mechanism: Neurotrophic agent with sigma-1 receptor agonist activity and additional neuroprotective mechanisms including anti-oxidant effects and enhancement of neurite outgrowth. The S1R component is one of several pharmacological activities [43].

Development trajectory: Toyama Chemical (Fujifilm Toyama Chemical) developed edonerpic for Alzheimer disease. A Phase 2 trial in Japan (SUNRISE-AD) in mild to moderate Alzheimer disease did not meet its primary endpoint but showed trends in subgroup analyses. A Phase 2 trial for post-stroke motor recovery (EUROS study) showed positive signals on upper limb function. The compound is in limited clinical development [43].

Novelty: Moderate. The neurotrophic enhancement mechanism is partially overlapping with the BDNF-enhancing effects of pridopidine but operates through distinct molecular pathways.

Effect size: Phase 2 Alzheimer data showed non-significant trends. Phase 2 stroke recovery data showed positive signals. Effect sizes are modest.

Promising potential: Low to moderate. Clinical development is limited. The compound is primarily a reference for understanding the intersection of S1R pharmacology and neurotrophic signaling.

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

Overall validation: Low. Phase 2 evidence is inconclusive. The compound has not advanced to Phase 3 in any indication.

Comparison to pridopidine: Edonerpic shares the S1R agonist mechanism and the BDNF-enhancing profile with pridopidine but has a less extensive clinical program and less clear mechanistic selectivity. Pridopidine has the advantages of a larger clinical database, clearer S1R selectivity at clinical doses (demonstrated by PET), and an active clinical development program.

12.6 Comparator summary

The five compounds occupy distinct positions in the sigma-1 receptor pharmacology landscape. **Blarcamesine** is the most clinically advanced S1R-active compound in Alzheimer disease and Rett syndrome, with a less selective but potentially complementary pharmacological profile. **Dextromethorphan** is the most clinically validated compound through its approved formulations (Nuedexta, Auvelity) but is fundamentally non-selective and unsuitable as a tool for S1R-specific neuroprotection research. **Fluvoxamine** has comparable S1R affinity to pridopidine but is an SSRI first and an S1R agonist second. **Cutamesine** is the closest pharmacological comparator (highly selective S1R agonist) but has been discontinued after negative Phase 2 trials. **Edonerpic** shares the neurotrophic and S1R mechanism but has limited clinical validation.

Pridopidine occupies a unique position in this comparator landscape: it is the most clinically advanced selective S1R agonist in neurodegenerative disease, the only S1R agonist with PET-confirmed selective receptor occupancy at clinical doses, the compound with the largest clinical safety database specifically in neurodegenerative disease populations (over 1,100 patients in randomized trials, up to 6.5 years of follow-up), and the only S1R agonist with an FDA-cleared Phase 3 trial program in ALS. Its principal limitation is the failure to meet primary endpoints in the overall populations of its Huntington disease trials, though the consistent subgroup signals and the mechanistic coherence of the S1R thesis support continued development.

The comparator landscape suggests that sigma-1 receptor agonism as a neuro-protective strategy has not yet produced a registration-level success in any neurodegenerative indication. Whether this reflects the mechanism (insufficient effect size for S1R agonism alone), the study designs (inappropriate endpoints or populations), or the compounds (insufficient potency, selectivity, or brain penetration) remains an open question. Pridopidine's PET-confirmed selective S1R occupancy, CYP2D6 auto-inhibition pharmacokinetics (reducing inter-individual variability), and consistent subgroup signals in both Huntington disease and ALS position it as the strongest current clinical candidate for resolving this question.

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