

RESEARCH MONOGRAPH . COMPOUND PROFILE

Dalzanemdor

A first-in-class synthetic analog of the endogenous cholesterol metabolite 24(S)-hydroxycholesterol, developed by Sage Therapeutics as an oral NMDA receptor positive allosteric modulator for cognitive impairment in Huntington's disease, Alzheimer's disease, and Parkinson's disease, with development discontinued in late 2024 following negative Phase 2 efficacy readouts across all three indications.

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ABSTRACT

Dalzanemdor (development code SAGE-718) is a first-in-class, orally bioavailable, small-molecule positive allosteric modulator (PAM) of the N-methyl-D-aspartate receptor (NMDAR), structurally derived from the endogenous cholesterol metabolite 24(S)-hydroxycholesterol (24(S)-HC). The compound was designed by Sage Therapeutics to address cognitive impairment in neurodegenerative disorders associated with NMDAR hypofunction, including Huntington's disease, Alzheimer's disease, and Parkinson's disease. Dalzanemdor potentiates NMDAR-mediated currents at all four GluN2 subunit-containing receptor assemblies (GluN1/GluN2A through GluN1/GluN2D) with equipotency, exhibiting EC₅₀ values in the low-nanomolar range (approximately 79 to 86 nM) and high intrinsic activity. The modulation increases NMDAR channel open probability without directly gating the receptor in the absence of endogenous glutamate, a feature that preserves physiological patterns of synaptic transmission and mitigates the excitotoxicity risk associated with direct NMDAR agonism.

The compound emerged from a research program initiated by the foundational discovery of Paul et al. (2013) demonstrating that 24(S)-HC, the major brain-specific cholesterol metabolite synthesized by CYP46A1, is a potent and selective endogenous NMDAR PAM at submicromolar concentrations. Medicinal chemistry optimization at Sage Therapeutics yielded dalzanemdor (compound 5 in the Hill et al. 2022 disclosure), a trifluoromethylated oxysterol with an optimized pharmacokinetic profile for oral dosing. In preclinical models, dalzanemdor

enhanced NMDAR-mediated long-term potentiation in hippocampal slices, increased excitatory postsynaptic potential amplitude in striatal medium spiny neurons, and reversed cognitive and behavioral deficits induced by NMDAR channel blockers and cholesterol depletion, without producing epileptiform activity or neurodegeneration on chronic dosing.

Phase 1 dose-finding studies (single-ascending dose, 0.35 to 3.0 mg; multiple-ascending dose, 0.5 to 1.0 mg for 14 days) in healthy participants and Huntington's disease participants established a pharmacokinetic profile characterized by oral absorption with median T_{max} of 4 to 7 hours, terminal half-life of approximately 28 to 40 hours after single doses extending to 99 to 125 hours after multiple doses, and dose-proportional exposures suitable for once-daily dosing. Exploratory cognitive assessments in Huntington's disease participants during the Phase 1 multiple-ascending dose study showed statistically significant improvement on the Two-Back Learning Task (executive function). Open-label Phase 2 studies in Parkinson's disease mild cognitive impairment (PARADIGM, n=18) and Alzheimer's disease (LUMINARY, n=26) generated signals of improvement on measures of executive function and learning. However, three subsequent randomized, double-blind, placebo-controlled Phase 2 studies (PRECEDENT in Parkinson's disease, LIGHTWAVE in Alzheimer's disease, DIMENSION in Huntington's disease) each failed to meet their primary cognitive endpoints. Sage Therapeutics discontinued all clinical development of dalzanemdor in November 2024.

This monograph documents the chemistry, structural pharmacology, oxysterol-site mechanism, human pharmacokinetics, the complete clinical trial inventory including

both positive open-label signals and negative controlled results, sourcing and handling considerations for research-grade material, adverse-event profile, and a comparative assessment of five NMDAR-targeting compounds against dalzanemdor on five competency standards. The compound is not approved by any regulatory authority. Research-grade dalzanemdor is available from chemical suppliers for in vitro and in vivo investigation of NMDAR positive allosteric modulation; 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: Dalzanemdor.

Development code: SAGE-718 (Sage Therapeutics). The development code is the canonical identifier in the published pharmacology, clinical, and regulatory literature and is the identifier under which all clinical trials were registered [2, 3, 4].

Chemical Abstracts Service registry number: 1629853-48-0.

PubChem Compound Identifier: CID 86305217.

International Union of Pure and Applied Chemistry name: (3S,8R,9S,10R,13R,14S,17R)-3,13-dimethyl-17-[(2R,5S)-6,6,6-trifluoro-5-hydroxy-5-methylhexan-2-yl]-2,4,7,8,9,10,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol.

Synonyms: SAGE-718, dalzanemdor, compound 5 (Hill et al. 2022 disclosure) [2].

1.2 Structural class and chemistry

Dalzanemdor is a synthetic oxysterol, structurally derived from the endogenous cholesterol metabolite 24(S)-hydroxycholesterol (24(S)-HC) [1, 2]. The compound retains the tetracyclic cyclopenta[a]phenanthrene steroid nucleus of cholesterol but carries two critical modifications relative to 24(S)-HC: a trifluoromethyl group appended to the side chain at the terminal position, and a tertiary alcohol with a methyl substituent at the C-5' position of the side chain. The trifluoromethyl modification was introduced during medicinal chemistry optimization to improve metabolic stability and oral pharmacokinetic properties while retaining NMDAR PAM activity [2]. The 3-beta-hydroxy group and the 3-alpha-methyl substituent on the A ring distinguish dalzanemdor from the natural cholesterol skeleton.

Molecular formula: C₂₇H₄₃F₃O₂.

Molecular weight: 456.6 g/mol (456.62 by high-resolution mass spectrometry, m/z 457.3254 [M+H]⁺).

Canonical SMILES: CC(CCC(C)(C(F)(F)F)O)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)(C)O)C)C.

InChIKey: BVBRUQYHUXKZMQ-JNVAYQLDSA-N.

Stereochemistry: Dalzanemdor contains seven defined stereocenters (3S,8R,9S,10R,13R,14S,17R) in the steroid nucleus, with an additional two stereocenters (2R,5S) in the modified side chain. The compound preserves the stereochemical configuration at positions equivalent to the natural cholesterol skeleton, consistent with the design rationale of mimicking 24(S)-HC at the NMDAR oxysterol binding site [1, 2]. The (S)-configuration at the side-chain hydroxyl corresponds to the 24(S)-configuration of the endogenous modulator. Investigators acquiring research-grade dalzanemdor should confirm stereochemical integrity by chiral high-performance liquid chromatography or by optical rotation measurement against a qualified reference standard.

1.3 Physical properties

Dalzanemdor is a white to off-white solid at room temperature. Detailed physical property data (solubility profile, melting point, partition coefficient) have not been published in the peer-reviewed literature. The compound was formulated as a solid oral tablet for clinical trials, consistent with acceptable aqueous solubility for oral absorption [4]. In research settings, the compound is supplied as a powder by chemical suppliers.

1.4 Structural relationship to 24(S)-hydroxycholesterol

The parent compound 24(S)-HC is the major brain-specific cholesterol metabolite, synthesized exclusively in neurons by the cytochrome P450 enzyme CYP46A1 from cholesterol in the endoplasmic reticulum of neuronal cell bodies and dendrites [1, 23]. Brain concentrations of 24(S)-HC are high (10 to 20 micrograms per gram of tissue, corresponding to approximately 25 micromolar) [1]. Paul et al. (2013) demonstrated that 24(S)-HC is a potent and selective positive allosteric modulator of NMDARs with an EC₅₀ of approximately 1.2 micromolar, while the structurally related synthetic analog SGE-201 exhibited approximately 10-fold higher potency (EC₅₀ approximately 0.11 micromolar) [1]. The structure-activity relationship established by Paul et al. and extended by Hill et al. (2022) demonstrated that the oxysterol side chain and the 3-beta-hydroxyl are critical pharmacophoric elements,

while the side-chain terminus tolerates fluorinated modifications that improve metabolic stability without loss of NMDAR PAM activity [1, 2]. Dalzanemdor (SAGE-718) represents the clinical-stage product of this optimization, with an EC₅₀ in the low-nanomolar range (approximately 79 to 86 nM depending on GluN2 subunit) and an oral pharmacokinetic profile suitable for once-daily human dosing [2, 3].

2. Abstract

Dalzanemdor (SAGE-718) is a first-in-class, orally bioavailable positive allosteric modulator of the N-methyl-D-aspartate receptor, designed as a synthetic analog of the endogenous cholesterol metabolite 24(S)-hydroxycholesterol [1, 2]. The compound potentiates NMDAR-mediated currents at all four GluN2 subunit-containing receptor assemblies with equipotency and high intrinsic activity, increasing channel open probability without directly gating the receptor in the absence of endogenous glutamate [3]. Dalzanemdor was developed by Sage Therapeutics for the treatment of cognitive impairment in neurodegenerative disorders associated with NMDAR hypofunction, including Huntington's disease, Alzheimer's disease, and Parkinson's disease.

Phase 1 dose-finding studies in healthy participants and Huntington's disease participants established favorable pharmacokinetic and safety profiles, with terminal half-life of approximately 28 to 40 hours after single doses, dose-proportional exposures, and tolerability characterized by mild adverse events (nausea, headache, somnolence) without seizure, neurotoxicity, or treatment-limiting toxicity [4]. Exploratory cognitive assessments in Phase 1 and open-label Phase 2 studies generated signals of improvement on measures of executive function and learning in Huntington's disease, Parkinson's disease, and Alzheimer's disease populations [4, 6, 7].

Three subsequent randomized, double-blind, placebo-controlled Phase 2 studies (PRECEDENT in Parkinson's disease, LIGHTWAVE in Alzheimer's disease with 174 participants, DIMENSION in Huntington's disease with 189 participants) each failed to demonstrate statistically significant improvement on their primary cognitive endpoints compared to placebo [10, 11, 13]. Dalzanemdor was generally well tolerated across all clinical studies, with no new safety signals and the majority of treatment-emergent adverse events rated mild to moderate in severity. Sage Therapeutics discontinued all clinical development of dalzanemdor in November 2024 following the negative DIMENSION readout [11].

This monograph reviews the structural chemistry, oxysterol pharmacology, human pharmacokinetics, preclinical pharmacology, the complete clinical trial inventory with both positive and negative results, and a comparative assessment of

NMDAR-targeting compounds in the cognitive impairment space. The compound is not approved by any regulatory authority and is available as a research-grade preparation for in vitro and in vivo investigation.

3. Discovery and Development History

3.1 Foundational discovery of oxysterol NMDAR modulation

The research program that produced dalzanemdor originated with the discovery by Paul et al. (2013) at Sage Therapeutics and Washington University that 24(S)-hydroxycholesterol (24(S)-HC), the major brain-specific cholesterol metabolite, is a potent and selective positive allosteric modulator of NMDARs [1]. This report, published in the Journal of Neuroscience, demonstrated that 24(S)-HC potentiates NMDAR-mediated excitatory postsynaptic currents in rat hippocampal neurons at submicromolar concentrations (EC50 approximately 1.2 micromolar) without affecting AMPA receptor or GABA-A receptor-mediated responses [1]. The selectivity and potency were unprecedented for an endogenous steroid modulator of NMDARs. Paul et al. also characterized a synthetic analog, SGE-201, with approximately 10-fold higher potency (EC50 approximately 0.11 micromolar), establishing the feasibility of medicinal chemistry optimization within the oxysterol scaffold [1].

A subsequent report by the same group (2014) demonstrated that structurally related oxysterols (25-hydroxycholesterol, 27-hydroxycholesterol) exert opposing (inhibitory) actions at NMDARs, establishing structure-activity relationships within the oxysterol class and underscoring the pharmacophoric specificity of the 24(S)-hydroxyl configuration [20].

3.2 Medicinal chemistry optimization and identification of SAGE-718

Hill et al. (2022) published the discovery of dalzanemdor (designated compound 5 in the publication) in the Journal of Medicinal Chemistry [2]. The optimization program sought a compound with the NMDAR PAM activity of 24(S)-HC and SGE-201 but with improved oral bioavailability, metabolic stability, and pharmacokinetic properties suitable for once-daily human dosing. Dalzanemdor was identified as a potent and high-intrinsic-activity NMDAR PAM with an optimized pharmacokinetic

profile [2]. The compound had completed Phase 1 single-ascending dose and multiple-ascending dose clinical trials at the time of publication and was entering Phase 2 clinical trials for cognitive impairment in Huntington's disease [2].

3.3 Clinical development program

Sage Therapeutics initiated Phase 1 clinical studies of dalzanemdor in 2018 to 2019 in healthy volunteers, assessing safety, tolerability, pharmacokinetics, and pharmacodynamic effects on NMDAR-mediated electrophysiology and magnetic resonance spectroscopy [4, 24]. The Phase 1 results, published by Koenig et al. (2024), established the pharmacokinetic and safety foundation for Phase 2 development [4].

In September 2020, Sage initiated the Phase 2 PARADIGM study (NCT04476017), an open-label evaluation of dalzanemdor 3 mg once daily for 14 days in participants with Parkinson's disease mild cognitive impairment [7, 12]. The PARADIGM Part A results, presented at the American Academy of Neurology 2022 Annual Meeting, reported improvements in executive function measures [7].

In February 2021, Sage initiated the Phase 2 LUMINARY study (NCT04602624), an open-label evaluation of dalzanemdor 3 mg once daily for 14 days in 26 participants with mild cognitive impairment or mild dementia due to Alzheimer's disease [6, 14]. The LUMINARY results, presented at the AAN 2022 Annual Meeting, reported a statistically significant improvement in the Montreal Cognitive Assessment (MoCA) of 2.3 points from baseline at Day 28 [6, 9].

In September 2021, the United States Food and Drug Administration granted Fast Track Designation to SAGE-718 for the treatment of Huntington's disease, recognizing the compound as addressing a serious condition with unmet medical need [8].

Between late 2021 and late 2022, Sage initiated four additional clinical studies: the PRECEDENT Phase 2 randomized trial in Parkinson's disease cognitive impairment (NCT05318937, dalzanemdor 1.2 mg daily for 6 weeks) [13, 39]; a 28-day Phase 2 study in Huntington's disease (NCT05107128, dalzanemdor 1.2 mg) [16]; the DIMENSION Phase 2 randomized trial in Huntington's disease cognitive impairment (NCT05358821, 12-week, dalzanemdor 1.2 mg reduced to 0.9 mg) [17]; the LIGHTWAVE Phase 2 randomized trial in Alzheimer's disease (NCT05619692, 12-week) [15]; and the PURVIEW open-label safety extension in Huntington's disease (NCT05655520) [18].

3.4 Phase 2 results and development discontinuation

In April 2024, Sage announced that the PRECEDENT study in Parkinson's disease cognitive impairment had missed its primary endpoint (WAIS-IV Coding Test) [13, 40]. The company discontinued development of dalzanemdor in Parkinson's disease.

On October 8, 2024, Sage announced topline results from the LIGHTWAVE study in Alzheimer's disease: dalzanemdor did not demonstrate a statistically significant difference from placebo on the primary endpoint (WAIS-IV Coding Test score at Day 84) in 174 randomized participants, and exploratory endpoints (RBANS total score, MoCA total score) showed no meaningful differences [10]. The company discontinued development of dalzanemdor in Alzheimer's disease.

On November 20, 2024, Sage announced topline results from the DIMENSION study in Huntington's disease: dalzanemdor did not demonstrate a statistically significant difference versus placebo on the primary endpoint (Symbol Digit Modalities Test at Day 84) in 189 randomized participants, and secondary endpoints showed no statistically significant or clinically meaningful differences [11]. The company announced that it did not plan further development of dalzanemdor and would close the ongoing PURVIEW open-label safety study [11].

The complete development trajectory of dalzanemdor therefore spans approximately six years from Phase 1 initiation (2018) through Phase 2 failure across all three neurodegenerative disease indications (2024), with FDA Fast Track Designation and positive open-label signals that were not confirmed in adequately powered controlled trials.

4. Molecular Pharmacology

4.1 NMDA receptor biology and the oxysterol modulatory site

The N-methyl-D-aspartate receptor is a heterotetrameric ligand-gated ion channel of the ionotropic glutamate receptor family, composed of two obligatory GluN1 subunits and two GluN2 subunits (GluN2A, GluN2B, GluN2C, or GluN2D) or, less commonly, GluN3 subunits [19]. The receptor requires simultaneous binding of glutamate (at GluN2 subunits) and glycine or D-serine (at GluN1 subunits) for activation, and is subject to voltage-dependent magnesium block at resting membrane potential. NMDAR activation produces calcium influx that triggers downstream signaling cascades essential for synaptic plasticity, long-term potentiation (LTP), learning, and memory [19]. NMDAR hypofunction is implicated in the cognitive impairment associated with neurodegenerative disorders including Huntington's disease, Alzheimer's disease, and Parkinson's disease, and in schizophrenia.

The oxysterol modulatory site is a pharmacologically distinct allosteric binding site on the NMDAR, identified through the work of Paul et al. (2013) [1]. This site is accessed by 24(S)-HC, the major brain cholesterol metabolite, and is distinct from the glutamate binding site, the glycine/D-serine binding site, the magnesium block site, the zinc inhibitory site, the polyamine modulatory site, and the neurosteroid inhibitory sites described for pregnenolone sulfate and related sulfated steroids [1, 19, 20]. The oxysterol site appears to be located within or near the transmembrane domain, consistent with the observation that oxysterol modulators may partition into the plasma membrane to access the NMDAR rather than binding at a direct aqueous-accessible site; this lipophilic access pathway explains the slow onset and offset kinetics of modulation by 24(S)-HC and its synthetic analogs [1, 22].

4.2 Dalzanemdor as an NMDAR positive allosteric modulator

Beckley et al. (2024) published the pharmacological characterization of dalzanemdor in the British Journal of Pharmacology, reporting in vitro and in vivo electrophysiological and behavioral findings [3]. The key pharmacological properties are:

Subunit equipotency. Dalzanemdor potentiated GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and GluN1/GluN2D NMDA receptor assemblies with equipotency [3]. EC50 values reported from the published characterization are approximately 86 nM for GluN1/GluN2A and approximately 79 nM for GluN1/GluN2B [3]. The equipotency across GluN2 subtypes mirrors the selectivity profile of the endogenous modulator 24(S)-HC, which also shows no significant GluN2-subtype preference [1], and distinguishes dalzanemdor from GluN2B-selective antagonists and GluN2A-selective modulators.

High intrinsic activity. Hill et al. (2022) described dalzanemdor as possessing "high intrinsic activity" at NMDARs [2], indicating that the compound approaches the maximum potentiation achievable by the endogenous oxysterol PAM at the same site, rather than functioning as a low-efficacy partial modulator.

Mechanism of channel modulation. Dalzanemdor increased the rate of unblock of the NMDAR open-channel blocker ketamine on GluN1/GluN2A receptors in vitro, providing evidence that the compound increases NMDAR channel open probability [3]. The primary mechanism by which neuroactive steroid NMDAR PAMs enhance NMDAR current is an increase in channel open probability without altering unitary conductance, as established for the related compounds SGE-301 and SGE-550 by Tang et al. (2023) [5].

Absence of direct channel gating. Dalzanemdor modulates NMDAR activity only in the presence of endogenous agonists (glutamate and glycine/D-serine); the compound does not directly gate the NMDAR channel or activate the receptor in the absence of agonist [3]. This property is critical for the therapeutic rationale: positive allosteric modulation preserves the temporal and spatial patterns of endogenous glutamatergic neurotransmission while enhancing receptor function at synapses where NMDARs are activated by physiological glutamate release, thereby avoiding the excitotoxicity associated with direct NMDAR agonism and the tonic receptor overstimulation that has produced adverse effects with glycine-site full agonists.

Electrophysiology in native tissue. Dalzanemdor increased NMDAR excitatory postsynaptic potential (EPSP) amplitude in striatal medium spiny neurons without affecting EPSP decay kinetics [3]. The increase in EPSP amplitude without prolongation of the synaptic current supports the model of increased channel open probability (more channels opening per synaptic event) rather than altered receptor desensitization or prolonged channel open time. The striatal medium spiny neuron is

a cell type of particular relevance to Huntington's disease, as degeneration of these neurons in the caudate and putamen is the neuropathological hallmark of the disease.

4.3 Overlapping binding site with 24(S)-hydroxycholesterol

Competition experiments reported in the published literature indicate that dalzanemdor and 24(S)-HC likely bind to overlapping sites on GluN1/GluN2A NMDARs [3]. When 24(S)-HC was added at concentrations exceeding its EC₅₀ by more than 100-fold, dalzanemdor produced only modest additional potentiation; as 24(S)-HC concentrations were decreased, dalzanemdor efficacy increased, consistent with competitive occupancy at the same or closely overlapping allosteric sites [3]. This finding supports the design rationale of dalzanemdor as a pharmacological surrogate for the endogenous oxysterol modulator.

4.4 Selectivity

Dalzanemdor is selective for NMDARs. The published characterization reports that the compound modulates NMDAR-mediated currents without affecting AMPA receptor-mediated or GABA-A receptor-mediated synaptic responses [1, 3]. The selectivity mirrors that of 24(S)-HC, for which Paul et al. (2013) demonstrated that NMDAR EPSC potentiation occurred without detectable effects on pharmacologically isolated AMPAR EPSCs or GABA-A PSCs [1]. This selectivity distinguishes oxysterol NMDAR PAMs from neurosteroids such as allopregnanolone and pregnenolone sulfate, which modulate multiple ligand-gated ion channels (GABA-A, glycine, and 5-HT₃ receptors) at overlapping concentration ranges.

4.5 Comparison to other neuroactive steroid NMDAR PAMs

Within the Sage Therapeutics oxysterol PAM program, dalzanemdor is the most advanced clinical candidate. Earlier synthetic analogs include SGE-201 (Paul et al. 2013, EC₅₀ approximately 0.11 micromolar) [1], SGE-301 (advanced through preclinical pharmacology and characterized as a rescue agent in anti-NMDAR encephalitis models) [34, 35], and SGE-550 (Tang et al. 2023, EC₅₀ 29 to 121 nM across GluN2 subtypes) [5]. Dalzanemdor's EC₅₀ of approximately 79 to 86 nM places it in the same

potency range as SGE-550 and approximately 10-fold more potent than SGE-201. All compounds in this series share the core oxysterol mechanism: allosteric potentiation of NMDAR channel open probability at a transmembrane-accessible site, without direct channel gating, with equipotency across GluN2 subtypes [1, 3, 5].

5. Pharmacokinetics

5.1 Absorption

Dalzanemdor is absorbed from the gastrointestinal tract after oral administration of solid tablets. In the Phase 1 single-ascending dose (SAD) study in healthy participants, median time to peak plasma concentration (T_{max}) ranged from 4.24 to 7.00 hours across doses of 0.35 to 3.0 mg, with maximum plasma concentrations (C_{max}) of 5.72 ng/mL at 0.35 mg, 11.15 ng/mL at 0.75 mg, 20.57 ng/mL at 1.5 mg, and 45.54 ng/mL at 3.0 mg [4].

Food effect. A dedicated food-effect cohort in the SAD study (0.75 mg fasted vs. fed) demonstrated that food modestly reduces dalzanemdor exposure: fasted C_{max} and AUC₀₋₂₄ (11.2 ng/mL and 144.4 ng $\cdot$ h/mL) *were approximately 1.3-fold higher than fed values (8.6 ng/mL and 112.6 ng $\cdot$ h/mL)*, and fasted AUC_{0-infinity} (358.4 ng $\cdot$ h/mL) *was approximately 1.7-fold higher than fed (204.9 ng $\cdot$ h/mL)* [4]. Fasted versus fed terminal half-life was 40.1 versus 24.6 hours [4]. Despite this modest food effect, clinical trials administered dalzanemdor with meals; the PARADIGM and LUMINARY studies specified administration with a meal containing approximately 30 grams of dietary fat.

Dose proportionality. In the SAD study, slope point estimates for the power model were near 1, and 95 percent confidence intervals contained 1, for both C_{max} and AUC, indicating dose-proportional exposure across the 0.35 to 3.0 mg range after single doses [4].

5.2 Distribution and accumulation

Preclinical distribution data, reported as unpublished in the Koenig et al. (2024) publication, include a brain-to-plasma ratio of 5.3 in rats and a brain terminal half-life at least as long as the plasma terminal half-life [4]. These data support meaningful central nervous system exposure consistent with the intended NMDAR target engagement.

Plasma protein binding, volume of distribution, and cerebrospinal fluid concentrations have not been formally published in the peer-reviewed literature. The high brain-to-plasma ratio and the lipophilic oxysterol structure suggest substantial tissue partitioning and brain penetration.

Accumulation with multiple dosing. In the multiple-ascending dose (MAD) study in healthy participants (0.5 and 1.0 mg daily for 14 days), dalzanemdor accumulated approximately 2.5- to 2.6-fold for C_{max} and 3.1-fold for AUC_{0-tau} relative to Day 1 values [4]. At 1.0 mg, Day 14 C_{max} was 41.2 ng/mL (versus 15.7 ng/mL on Day 1) and AUC₀₋₂₄ was 661.8 ngh/mL (*versus 210.7 ngh/mL* on Day 1) [4]. Steady state was achieved after approximately 11 days in healthy participants and 13 days in Huntington's disease participants [4]. The accumulation and time to steady state are consistent with the long terminal half-life observed after multiple dosing.

Comparison of healthy and HD exposures. After single doses of dalzanemdor 1.0 mg, the Huntington's disease to healthy-participant ratio of geometric least-squares mean AUC_{0-last} was 0.63 (90% CI: 0.47 to 0.85), indicating approximately 37 percent lower systemic exposure in Huntington's disease participants [4]. The mechanism of this reduced exposure is not established; possibilities include altered absorption, distribution, or metabolism associated with Huntington's disease pathophysiology.

5.3 Metabolism

Dalzanemdor is metabolized hepatically. Preclinical data indicate low hepatic clearance [4]. Specific cytochrome P450 isoforms responsible for dalzanemdor metabolism, metabolite identification, and the contribution of individual CYP enzymes have not been published in the peer-reviewed literature. Given the oxysterol structure, CYP3A4-mediated oxidation is plausible by analogy to cholesterol and oxysterol metabolism, but this has not been confirmed for dalzanemdor specifically. Investigators requiring metabolic pathway data should consult the sponsor's regulatory filings, which may contain this information.

5.4 Elimination

The terminal elimination half-life of dalzanemdor is notably prolonged and increases with multiple dosing. After single doses in healthy participants, median terminal half-life ranged from 27.92 hours (0.35 mg) to 40.10 hours (0.75 mg) [4]. After 14 days of multiple dosing, median terminal half-life was 99 hours at 0.5 mg and 118

hours at 1.0 mg in healthy participants, and 125 hours at 1.0 mg in Huntington's disease participants [4]. The prolongation of the terminal half-life with multiple dosing likely reflects accumulation in deep tissue compartments (consistent with the high brain-to-plasma ratio and the lipophilic steroid structure) and time-dependent redistribution kinetics.

Exposure after multiple doses was more than dose-proportional: comparing 0.5 mg with 1.0 mg in healthy participants, geometric least-squares mean ratios for AUC_{0-last}, AUC₀₋₂₄, and C_{max} indicated that the exposure increase exceeded the 2-fold dose difference [4].

Routes of elimination (renal versus biliary) and the proportion of unchanged drug excreted have not been published.

5.5 Preclinical pharmacokinetics

In preclinical species, dalzanemdor demonstrated oral bioavailability of 30 to 73 percent in dogs, low hepatic clearance, and favorable central nervous system penetration (brain-to-plasma ratio 5.3 in rats) [4]. These preclinical properties supported the selection of the oral route of administration and once-daily dosing frequency for clinical development.

6. Preclinical Pharmacology

6.1 In vitro electrophysiology

The primary in vitro pharmacology of dalzanemdor was characterized by Beckley et al. (2024) using patch-clamp electrophysiology in heterologous expression systems and in native brain tissue [3].

In recombinant NMDAR expression systems, dalzanemdor potentiated agonist-evoked currents at GluN1/GluN2A, GluN1/GluN2B, GluN1/GluN2C, and GluN1/GluN2D receptor assemblies with equipotency [3]. The potentiation was manifest as an increase in current amplitude consistent with increased channel open probability; single-channel conductance was not altered [3, 5].

In acute brain slices, dalzanemdor increased NMDAR-mediated excitatory post-synaptic potential amplitude in striatal medium spiny neurons without affecting EPSP decay kinetics [3]. This finding is of direct relevance to Huntington's disease, where medium spiny neuron dysfunction and degeneration are the primary neuropathological substrates.

Dalzanemdor enhanced NMDAR-mediated long-term potentiation (LTP) in hippocampal slices, providing electrophysiological evidence that the compound augments the synaptic plasticity mechanism most directly linked to learning and memory [3]. The LTP enhancement is consistent with the pharmacological rationale for cognitive enhancement through NMDAR positive allosteric modulation.

6.2 In vivo behavioral and cognitive models

Beckley et al. (2024) reported that dalzanemdor ameliorated behavioral deficits in two distinct NMDAR hypofunction models [3]:

Phencyclidine-induced social deficit model. Subchronic administration of phencyclidine (PCP), a non-competitive NMDAR channel blocker, produces social interaction deficits in rodents that model aspects of cognitive and negative symptom domains observed in schizophrenia and neurodegenerative diseases. Dalzanemdor reversed the PCP-induced social deficits, providing in vivo evidence that the compound can rescue behavior associated with NMDAR hypofunction [3].

Cholesterol depletion model. Inhibition of 7-dehydrocholesterol reductase (the terminal enzyme in the Kandutsch-Russell cholesterol biosynthesis pathway) depletes brain cholesterol and, consequently, its metabolite 24(S)-HC, producing NMDAR hypofunction through loss of endogenous oxysterol PAM tone. Dalzanemndor reversed the behavioral and electrophysiological deficits induced by cholesterol depletion, providing a direct test of the hypothesis that pharmacological restoration of oxysterol-site NMDAR modulation can compensate for reduced endogenous 24(S)-HC [3].

Additionally, dalzanemndor reversed behavioral and cognitive deficits in mice and rats treated with NMDAR channel blockers, demonstrating generalizability of the rescue pharmacology across multiple models of NMDAR hypofunction [3].

6.3 Safety pharmacology

Dalzanemndor demonstrated a favorable preclinical safety profile in safety pharmacology assessments [3, 4]:

Seizure threshold. The compound did not produce epileptiform activity in a seizure model, addressing the theoretical concern that NMDAR potentiation could lower seizure threshold through enhanced glutamatergic excitatory neurotransmission [3]. This finding was confirmed in clinical Phase 1 studies, where independent review of EEGs at the highest dose tested (3.0 mg) did not identify epileptiform activity [4].

Chronic dosing neurotoxicity. Dalzanemndor did not produce neurodegeneration following chronic dosing in preclinical studies [3]. This is an important safety finding because excessive NMDAR activation, as produced by excitotoxic concentrations of glutamate, can cause neuronal cell death through calcium-mediated excitotoxicity. The absence of neurotoxicity on chronic dosing is consistent with the positive allosteric modulator mechanism: the compound amplifies endogenous glutamatergic signaling without producing tonic or excessive receptor activation.

6.4 Limitations of the published preclinical record

The full preclinical pharmacology of dalzanemndor is published only in the Beckley et al. (2024) report, which is a comprehensive single publication [3]. The primary paper is behind a paywall; the accessible abstract and summary sections provide the findings described above but do not include dose-response curves, specific

doses administered in each in vivo model, or detailed statistical analyses for the behavioral endpoints. The Hill et al. (2022) discovery paper describes the compound selection process but does not provide detailed in vivo pharmacology [2]. Investigators requiring granular preclinical data (specific doses, ED50 values in behavioral models, dose-response relationships, species-specific PK/PD correlations) should consult the full text of the Beckley et al. report or the sponsor's regulatory filings.

7. Clinical Evidence Base

The clinical evidence base for dalzanemdor comprises Phase 1 dose-finding studies in healthy participants and Huntington's disease participants; three open-label Phase 2 studies (PARADIGM in Parkinson's disease, LUMINARY in Alzheimer's disease, and a 28-day Huntington's disease study); and three randomized, double-blind, placebo-controlled Phase 2 studies (PRECEDENT in Parkinson's disease, LIGHTWAVE in Alzheimer's disease, DIMENSION in Huntington's disease). All three controlled Phase 2 studies failed their primary cognitive endpoints. This section presents both the positive open-label signals and the negative controlled results with equal weight, as the full evidence record is necessary for investigator assessment. The compound is not approved by any regulatory authority and is presented for research use only.

7.1 Phase 1 single-ascending dose study

Koenig et al. (2024) reported a first-in-human, Phase 1, double-blind, placebo-controlled, single-ascending dose study in healthy participants [4]. Five cohorts were enrolled: Cohorts 1 through 4 received dalzanemdor at 0.35, 0.75, 1.5, and 3.0 mg respectively, with sentinel dosing (first two participants randomized 1:1 to active and placebo) followed by the remaining participants randomized 5:1 to active or placebo, for six active and two placebo per cohort. Cohort 5 received 0.75 mg for food-effect assessment in an open-label design [4]. Dalzanemdor was well tolerated at all doses; all treatment-emergent adverse events were mild and resolved by study end [4].

7.2 Phase 1 multiple-ascending dose study

The MAD study enrolled three cohorts: healthy participants at 0.5 mg (Cohort 1, n=12, 9 active and 3 placebo) and 1.0 mg (Cohort 2, n=12, 9 active and 3 placebo) once daily for 14 days in a double-blind design, and Huntington's disease participants at 1.0 mg (Cohort 3, n=6) once daily for 14 days in an open-label design [4].

Exploratory cognitive assessments using the CogState battery revealed differential performance patterns between healthy and Huntington's disease participants [4]. At baseline, Huntington's disease participants performed significantly worse than healthy participants on the One-Back Learning Task ($p=0.040$), the Two-Back Learning Task ($p<0.001$, effect size $d=2.106$), and the Stop Signal Reaction Test ($p=0.003$, effect size $d=1.499$) [4]. On treatment with dalzanemdor, Huntington's disease participants improved from baseline on the Two-Back Learning Task at all time points, with statistically significant improvement on Days 8, 10, 12, and 14 compared to healthy participants receiving the same dose [4]. A trend toward improvement on the Groton Maze Learning Test was observed but was not statistically significant [4]. No clinically meaningful changes were observed on the Detection Test [4].

The cognitive improvement in Huntington's disease participants on the Two-Back Learning Task (a measure of working memory and executive function) provided the initial efficacy signal that supported Phase 2 development. However, the open-label design and small sample size ($n=6$) preclude definitive efficacy conclusions from this Phase 1 cohort.

7.3 PARADIGM study (Parkinson's disease, open-label)

The PARADIGM study (NCT04476017) was an open-label Phase 2 study evaluating dalzanemdor 3 mg once daily for 14 days in 18 participants with Parkinson's disease mild cognitive impairment (PD-MCI), ages 50 to 75 years, with baseline MoCA scores of 20 to 25 [7, 12]. Results, presented at the American Academy of Neurology 2022 Annual Meeting, reported improved performance at Day 14 compared to baseline on tests of executive functioning including Multitasking, Stockings of Cambridge, Spatial Working Memory, Digit Symbol Substitution, and the Two-Back Test [7]. An emerging signal of improved performance on tests of learning and memory (Paired Associates, Pattern Recognition, Verbal Memory) was observed, but no appreciable effect was detected on measures of simple attention and psychomotor speed [7]. The most common adverse events were headache, somnolence, and dizziness; no serious adverse events or deaths were reported, and no treatment-emergent adverse events led to study drug discontinuation [7].

7.4 LUMINARY study (Alzheimer's disease, open-label)

The LUMINARY study (NCT04602624) was an open-label Phase 2 study evaluating dalzanemdor 3 mg once daily for 14 days in 26 participants with mild cognitive impairment or mild dementia due to Alzheimer's disease, ages 50 to 80 years, with baseline MoCA scores of 15 to 24 [6, 14]. Results, presented at the American Academy of Neurology 2022 Annual Meeting, reported a statistically significant improvement of 2.3 points on the Montreal Cognitive Assessment from baseline at Day 28 [6, 9]. Improvements from baseline were observed at Day 14 on multiple tests of executive functioning (Digit Symbol Substitution, Multitasking, One Touch Stockings, Spatial Working Memory, Two-Back Test) and on tests of learning and memory (Pattern Recognition Memory, Verbal Recognition Memory) [6, 9].

Eight treatment-emergent adverse events were reported in 7 of 26 patients (26.9 percent); all were mild or moderate in severity, and six were considered treatment-related [6]. No serious adverse events or deaths were reported.

The LUMINARY study, as an open-label design with 26 participants and no placebo comparator, does not provide evidence of treatment effect attributable to dalzanemdor rather than to placebo response, practice effects on cognitive testing, or regression to the mean. The positive signals informed the design of the subsequent LIGHTWAVE controlled trial.

7.5 PRECEDENT study (Parkinson's disease, randomized controlled)

The PRECEDENT study (NCT05318937) was a Phase 2, randomized, placebo-controlled study of dalzanemdor 1.2 mg once daily for 6 weeks in participants with Parkinson's disease cognitive impairment [13, 39]. The planned enrollment was approximately 76 participants; the primary endpoint was the WAIS-IV Coding Test.

In April 2024, Sage Therapeutics announced that the PRECEDENT study had missed its primary endpoint [40]. Detailed results (effect sizes, secondary endpoints, subgroup analyses) have not been published in peer-reviewed form. The company discontinued development of dalzanemdor in Parkinson's disease following this negative readout.

7.6 LIGHTWAVE study (Alzheimer's disease, randomized controlled)

The LIGHTWAVE study (NCT05619692) was a 12-week, Phase 2, randomized, double-blind, placebo-controlled study evaluating dalzanemdor in 174 randomized participants with mild cognitive impairment or mild dementia due to Alzheimer's disease [10, 15]. The primary endpoint was the WAIS-IV Coding Test score at Day 84.

Topline results announced October 8, 2024, demonstrated that dalzanemdor did not achieve a statistically significant difference from placebo on the primary endpoint [10]. Analyses of exploratory endpoints including RBANS total score and MoCA total score did not demonstrate meaningful differences between dalzanemdor and placebo groups [10]. Dalzanemdor was generally well tolerated, with the majority of treatment-emergent adverse events mild to moderate in severity and no new safety signals [10].

The negative LIGHTWAVE result is notable in context: the earlier LUMINARY open-label study in the same patient population had generated a 2.3-point MoCA improvement signal, which was not replicated under controlled conditions. The discrepancy is consistent with the well-documented contribution of placebo response, practice effects, and regression to the mean in open-label cognitive trials in Alzheimer's disease populations.

7.7 DIMENSION study (Huntington's disease, randomized controlled)

The DIMENSION study (NCT05358821) was a 12-week, Phase 2, randomized, double-blind, placebo-controlled study evaluating dalzanemdor in 189 randomized participants with cognitive impairment associated with Huntington's disease [11, 17]. The dosing regimen was dalzanemdor 1.2 mg once daily for the first month, reduced to 0.9 mg once daily for the subsequent two months. The primary endpoint was the change from baseline on the Symbol Digit Modalities Test (SDMT) at Day 84.

Topline results announced November 20, 2024, demonstrated that dalzanemdor did not achieve a statistically significant difference versus placebo on the primary endpoint [11]. Analyses of secondary endpoints did not demonstrate statistically significant or clinically meaningful differences between dalzanemdor and placebo

[11]. Dalzanemdor was generally well tolerated, with the majority of treatment-emergent adverse events mild to moderate in severity and no new safety signals [11].

Based on these results, Sage Therapeutics announced discontinuation of all dalzanemdor development and closure of the PURVIEW open-label safety study (NCT05655520) [11, 18].

7.8 Summary of regulatory status

Dalzanemdor received FDA Fast Track Designation for the treatment of Huntington's disease in September 2021 [8]. The compound is not approved by any regulatory authority. All clinical development has been discontinued as of November 2024.

8. Sourcing and Quality Verification

Dalzanemdor has never been approved as a pharmaceutical product; no pharmaceutical-grade formulation is commercially available. The compound was manufactured by Sage Therapeutics for clinical trial use as a solid oral tablet (3 mg dose in PARADIGM and LUMINARY; 1.2 mg and 0.9 mg doses in later Phase 2 trials) but this clinical-trial supply is not available to external investigators.

Research-grade dalzanemdor is available from multiple chemical and pharmaceutical research suppliers, including BenchChem, TargetMol, ProbeChem, and AbMole, typically in milligram quantities (1 mg, 5 mg, or custom bulk) as the free base or as specified salt forms [CAS 1629853-48-0]. Pricing is in the moderate-to-expensive range consistent with novel research-grade oxysterol compounds.

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

- High-performance liquid chromatography (HPLC) area-percent purity assessment, ideally greater than 95 percent.
- High-resolution mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ m/z 457.3254 for $C_{27}H_{43}F_3O_2$).
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C NMR) for structural confirmation, with comparison to published spectral data from the Hill et al. (2022) disclosure [2].
- Chiral HPLC or polarimetry to confirm stereochemical integrity at the nine defined stereocenters.
- Assessment of residual solvents by gas chromatography.

Third-party analytical laboratories providing independent verification of vendor certificates of analysis are recommended for any investigation where dose-response precision or mechanism-of-action interpretation depends on compound identity and purity. The research-grade dalzanemdor market is recent and small; lot-to-lot variability may exceed that of well-established research compounds, and independent on-receipt analytical confirmation is strongly recommended.

9. Reconstitution and Handling

Published handling data for dalzanemdor are limited. The compound was administered in clinical trials as a solid oral tablet, indicating stability in solid oral dosage form under standard pharmaceutical storage conditions.

For in vitro research applications, dalzanemdor is supplied as a solid powder and is reconstituted in appropriate solvents. Given the lipophilic oxysterol structure, the compound is expected to dissolve readily in dimethyl sulfoxide (DMSO) at stock concentrations of 10 to 50 mM for in vitro pharmacology experiments. Aqueous solubility of the free base is expected to be limited, consistent with the steroid structural class; for cell-based assays, serial dilution from DMSO stock into aqueous media is recommended, with final DMSO concentrations held below 0.1 to 0.5 percent to avoid solvent effects on NMDAR function.

For in vivo research applications in rodent studies, formulation in standard oral vehicles (methylcellulose suspension, cyclodextrin solutions, or polyethylene glycol-based vehicles) is appropriate for oral gavage administration, consistent with the preclinical studies reported by Beckley et al. (2024) [3].

Storage of solid dalzanemdor at minus 20 degrees Celsius under desiccated conditions is recommended for long-term stability. DMSO stock solutions should be aliquoted for single use and stored at minus 20 degrees Celsius; repeated freeze-thaw cycles should be avoided until stability data specific to dalzanemdor are available. Light protection is a reasonable precaution given the unsaturated steroid nucleus, although formal photostability data have not been published.

Investigators should treat these handling recommendations as starting points and verify stability under their specific laboratory conditions, as compound-specific degradation profiles for dalzanemdor have not been published.

10. Stack Interactions and Combinations

10.1 Metabolic interactions

Formal drug-drug interaction studies for dalzanemdor have not been published. The specific CYP enzymes responsible for dalzanemdor metabolism are not identified in the peer-reviewed literature [4]. As an oxysterol derivative with a steroid nucleus, dalzanemdor is plausibly metabolized by CYP3A4 and potentially by CYP2D6 or other hepatic CYP enzymes, by analogy to cholesterol and related oxysterol metabolism. Until formal metabolic studies are published, investigators should exercise caution with concurrent administration of strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir) or strong CYP3A4 inducers (rifampin, carbamazepine, phenytoin, St. John's wort), as these agents could alter dalzanemdor exposure in unpredictable directions.

The food effect observed in Phase 1 (approximately 1.3- to 1.7-fold reduction in exposure with food) [4] indicates that meal timing and composition may influence dalzanemdor pharmacokinetics. In clinical trials, the compound was administered with a meal containing approximately 30 grams of dietary fat.

10.2 Pharmacodynamic interactions at the NMDAR

NMDAR channel blockers. Dalzanemdor's mechanism of action (increasing NMDAR channel open probability) is pharmacologically opposed by NMDAR channel blockers such as memantine, ketamine, phencyclidine, and dextromethorphan. Concurrent administration of dalzanemdor with memantine (an FDA-approved Alzheimer's disease treatment) would produce competing pharmacological effects at the same receptor. The clinical significance of this interaction has not been studied; investigators should consider whether concurrent NMDAR blockade would confound the interpretation of dalzanemdor's effects in research settings.

NMDAR glycine-site modulators. Concurrent administration with glycine, D-serine, D-cycloserine, or other glycine-site agonists or partial agonists could produce additive NMDAR potentiation through complementary allosteric mechanisms

(glycine-site enhancement plus oxysterol-site enhancement). The combination has not been studied clinically but may be of interest for fundamental NMDAR pharmacology research.

Other oxysterol NMDAR PAMs. Concurrent administration with other oxysterol-site PAMs (SGE-301, SGE-550, or 24(S)-HC) would produce competitive or additive effects at the same allosteric site. The competition experiments reported by Beckley et al. (2024) indicate that dalzanemdor and 24(S)-HC occupy overlapping sites [3]; concurrent administration may therefore not produce additive potentiation beyond the maximum achievable by either compound alone.

10.3 Combinations of potential research interest

Cholinesterase inhibitors. Concurrent donepezil, rivastigmine, or galantamine could produce complementary procognitive effects through NMDAR potentiation (dalzanemdor) plus cholinergic enhancement (cholinesterase inhibitor). This combination is of theoretical interest for Alzheimer's disease research, analogous to the clinical combination of memantine with cholinesterase inhibitors.

Glutamatergic agents. The interaction between dalzanemdor and agents that modulate glutamate release (lamotrigine, riluzole) or glutamate transporter function has not been characterized but is a plausible line of research for understanding the therapeutic window of NMDAR positive allosteric modulation.

10.4 Contraindicated combinations

Agents with seizure-lowering potential. Although dalzanemdor did not produce seizures or epileptiform activity in preclinical models or in clinical Phase 1 at doses up to 3.0 mg [3, 4], the theoretical concern that NMDAR potentiation could lower seizure threshold warrants caution with concurrent pro-convulsant agents in research settings.

11. Adverse Events and Safety Signal

11.1 Phase 1 safety profile

The Phase 1 program established a favorable safety profile for dalzanemdor at doses of 0.35 to 3.0 mg (single dose) and 0.5 to 1.0 mg (14 days of multiple dosing) [4].

In the SAD study, eight treatment-emergent adverse events (TEAEs) were reported in participants receiving dalzanemdor (Cohort 2 at 0.75 mg, n=1; Cohort 4 at 3.0 mg, n=3; Cohort 5 at 0.75 mg, n=4), and three TEAEs were reported with placebo [4]. TEAEs of nausea, headache, and somnolence were reported as related to the study drug. All TEAEs were mild and resolved by the study end [4].

In the MAD study in healthy participants, three TEAEs were reported in those receiving dalzanemdor (Cohort 1 at 0.5 mg, n=1; Cohort 2 at 1.0 mg, n=2), with orthostatic hypotension reported as related to the study drug [4].

In the MAD study in Huntington's disease participants (Cohort 3, 1.0 mg for 14 days), no TEAEs were reported [4].

No deaths, serious adverse events, or TEAE-related treatment discontinuations or study withdrawals were reported across the entire Phase 1 program [4].

11.2 Cardiovascular and neurological safety

No clinically significant findings were observed in laboratory parameters, vital signs, electrocardiograms (ECGs), or electroencephalograms (EEGs) in either the SAD or MAD study [4].

In the SAD study, no clinical signs of convulsions occurred at any dose. An independent review of EEGs in Cohort 4 (the first eight participants receiving the highest dose of dalzanemdor at 3.0 mg) did not identify epileptiform activity [4]. This finding addresses the theoretical concern that NMDAR positive allosteric modulation could lower seizure threshold.

No participants reported suicidal ideation or behavior at baseline or at any time point as measured by the Columbia Suicide Severity Rating Scale (C-SSRS) [4].

11.3 Open-label Phase 2 safety

In the LUMINARY study (Alzheimer's disease, 26 participants, 3 mg daily for 14 days), 8 TEAEs were reported in 7 patients (26.9 percent); all were mild or moderate in severity, and 6 were considered treatment-related [6]. No serious adverse events or deaths were reported.

In the PARADIGM study Part A (Parkinson's disease, 18 participants, 3 mg daily for 14 days), the most common adverse events were headache, somnolence, and dizziness. No serious adverse events or deaths were reported, and no TEAEs led to study drug discontinuation or study withdrawal [7].

11.4 Controlled Phase 2 safety

In the LIGHTWAVE study (Alzheimer's disease, 174 participants, 12 weeks), dalzanemdor was generally well tolerated with no new safety signals observed; the majority of treatment-emergent adverse events were mild to moderate in severity [10].

In the DIMENSION study (Huntington's disease, 189 participants, 12 weeks), dalzanemdor was generally well tolerated with no new safety signals observed; the majority of treatment-emergent adverse events were mild to moderate in severity [11].

Detailed adverse-event incidence tables from the LIGHTWAVE and DIMENSION studies have not been published in the peer-reviewed literature as of the present monograph date. The topline press releases do not provide individual adverse-event rates or system-organ-class breakdowns. Investigators requiring specific adverse-event frequencies should consult the clinical study reports when they become available through regulatory filings.

11.5 Aggregate safety assessment

Across all published clinical studies (Phase 1 and Phase 2), dalzanemdor demonstrated a consistently favorable safety profile. No treatment-related serious adverse events, no seizures or epileptiform EEG activity, no suicidal ideation or behavior,

and no clinically significant laboratory, vital sign, or ECG abnormalities were reported. The most common treatment-related adverse events across studies were headache, somnolence, dizziness, nausea, and orthostatic hypotension, all of mild to moderate severity. No treatment-emergent adverse events led to study drug discontinuation in any published study. The favorable safety profile was maintained across doses ranging from 0.35 mg (single dose) to 3.0 mg (14 days) and across treatment durations up to 12 weeks.

The absence of seizures and neurotoxicity is notable given the theoretical concern that NMDAR positive allosteric modulation could enhance glutamatergic excitotoxicity. The favorable safety profile is consistent with the allosteric mechanism, which amplifies endogenous receptor activation without producing tonic or excessive NMDAR stimulation.

12. Comparative Assessment

This section presents a structured comparative assessment of five NMDAR-targeting compounds against dalzanemdor, evaluated on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The comparators were selected to represent the principal pharmacological strategies for NMDAR modulation in cognitive impairment: positive allosteric modulation at the oxysterol site (SGE-301), glycine-site partial agonism (D-cycloserine, rapastinel), glycine-site modulation with novel mechanism (NYX-458), and NMDAR uncompetitive antagonism (memantine).

12.1 Memantine

Mechanism: Uncompetitive, voltage-dependent, low-affinity, open-channel blocker of the NMDAR. Memantine preferentially blocks excessive tonic NMDAR activation (attributed to excitotoxic glutamate levels in neurodegeneration) while permitting phasic synaptic NMDAR activation required for learning and memory, owing to its fast off-rate kinetics [25, 26]. The mechanism is pharmacologically opposite to dalzanemdor's positive allosteric modulation; memantine reduces NMDAR activity while dalzanemdor enhances it.

Development trajectory: Memantine (Namenda) was developed by Merz Pharmaceuticals and Forest Laboratories. It received FDA approval in 2003 for the treatment of moderate-to-severe Alzheimer's disease, based on the pivotal Reisberg et al. (2003) trial demonstrating clinically significant benefit on the Severe Impairment Battery and on the modified ADCS-ADL scale in 252 patients with moderate-to-severe Alzheimer's disease over 28 weeks [26]. An extended-release formulation (Namenda XR, 28 mg once daily) was subsequently approved. Memantine is the only NMDAR-targeting drug approved by the FDA for cognitive impairment.

Novelty: 2/5. The mechanism is well characterized and the compound has been commercially available for over two decades. The concept is mature.

Effect size: 2/5. Phase 3 trials demonstrated statistically significant but clinically modest benefits in moderate-to-severe Alzheimer's disease. Effect sizes on cognitive endpoints are small (Cohen's d approximately 0.2 to 0.3), and the clinical relevance

of the benefit has been debated [26]. Memantine has not demonstrated efficacy in mild Alzheimer's disease or in Huntington's or Parkinson's disease cognitive impairment.

Promising potential: 3/5. As an approved drug with established clinical use, memantine has defined its clinical ceiling. Its relevance to the dalzanemdor indication space is limited; memantine addresses a different severity stratum (moderate-to-severe) and a different pharmacological direction (antagonism versus agonism).

Side-effect profile: 4/5. Memantine is well tolerated at approved doses. Common adverse events (dizziness, headache, constipation, confusion) are mild and infrequent. The favorable safety profile is attributed to the low-affinity, voltage-dependent channel-blocking mechanism that avoids the dissociative and psychotomimetic effects of high-affinity NMDAR antagonists [25].

Overall validation: 4/5. Memantine is the most clinically validated NMDAR-targeting compound, with FDA approval, extensive clinical experience, and a robust safety database. However, the clinical benefit is modest and limited to moderate-to-severe Alzheimer's disease.

Comparison to dalzanemdor: Memantine and dalzanemdor target the same receptor through pharmacologically opposite mechanisms (antagonism versus positive allosteric modulation). Memantine is the only FDA-approved NMDAR-targeting drug; dalzanemdor was the first clinical-stage NMDAR PAM. The clinical failure of dalzanemdor does not validate memantine's mechanism over positive allosteric modulation in early-stage cognitive impairment, as the two compounds address different disease severities and different aspects of NMDAR dysfunction.

12.2 NYX-458

Mechanism: NMDAR modulator acting at the glycine modulatory site as a functional partial agonist. NYX-458 is a member of the Aptinyx platform of spirocyclic beta-lactam NMDAR modulators that enhance synaptic plasticity through a mechanism distinct from direct agonism or antagonism [27, 28].

Development trajectory: Aptinyx developed NYX-458 for Parkinson's disease mild cognitive impairment and Lewy body dementia cognitive impairment. Bhatt et al. (2020) demonstrated that NYX-458 improves cognitive performance in a chronic low-dose MPTP primate model of Parkinson's disease, with benefits in attention, working memory, executive function, and visuospatial learning [27]. A

Phase 2 clinical trial (NCT04148391) evaluated NYX-458 in participants with mild cognitive impairment or mild dementia due to Parkinson's disease or Lewy body dementia [37].

Novelty: 4/5. The glycine-site functional partial agonist mechanism is distinct from both the oxysterol PAM mechanism of dalzanemdor and the channel-blocking mechanism of memantine. The spirocyclic beta-lactam chemistry is structurally novel.

Effect size: 2/5. Preclinical cognitive efficacy in the primate PD model is encouraging but human effect-size data are limited and early-stage.

Promising potential: 2/5. Aptinyx entered bankruptcy proceedings in 2023; the clinical development status of NYX-458 is uncertain.

Side-effect profile: 3/5. Preclinical safety has been reported as adequate. Human safety data are limited.

Overall validation: 2/5. Preclinical data are promising but human clinical validation is incomplete.

Comparison to dalzanemdor: NYX-458 and dalzanemdor both target NMDAR-mediated cognitive impairment in Parkinson's disease through different allosteric mechanisms (glycine site versus oxysterol site). Both compounds generated preclinical cognitive efficacy signals but neither has produced positive controlled clinical trial results in the target population. NYX-458's glycine-site mechanism is pharmacologically complementary to the oxysterol-site mechanism and could theoretically be combined with an oxysterol PAM for additive NMDAR potentiation.

12.3 D-Cycloserine

Mechanism: Partial agonist at the glycine modulatory site of the NMDAR. D-cycloserine is a cyclic analog of D-alanine that acts as a partial agonist at the glycine binding site of the GluN1 subunit, producing submaximal NMDAR activation that is sufficient for procognitive and plasticity-enhancing effects without the excitotoxicity associated with full agonism [32, 33].

Development trajectory: D-cycloserine is approved as an antibiotic for the treatment of tuberculosis (Seromycin). Its NMDAR-modulating properties were identified in the 1990s, and it has been studied extensively as a cognitive enhancer in

Alzheimer's disease, schizophrenia, and as an augmentation agent for cognitive behavioral therapy. Tsai et al. (1996) demonstrated that D-cycloserine at 15 mg twice daily for 10 weeks significantly enhanced implicit memory in 108 Alzheimer's disease patients in a randomized, placebo-controlled trial [32]. Subsequent larger trials at higher doses did not replicate the cognitive benefit, likely owing to dose-dependent receptor desensitization at the glycine site [33]. In schizophrenia, intermittent D-cycloserine dosing has shown benefit for negative symptoms and cognitive remediation augmentation [33].

Novelty: 1/5. The compound and mechanism are well established; research interest dates to the 1990s.

Effect size: 2/5. Modest and inconsistent effects on cognition across multiple clinical trials. The dose-response relationship is non-monotonic (inverted U), and the optimal dose for cognitive enhancement is narrow.

Promising potential: 2/5. Not in active commercial development for cognitive indications. Remains a research tool for NMDAR glycine-site pharmacology and for cognitive behavioral therapy augmentation.

Side-effect profile: 4/5. Well tolerated at the doses used for NMDAR modulation (5 to 50 mg). Higher antibiotic doses (250 to 1000 mg) produce more frequent adverse events.

Overall validation: 3/5. Extensive clinical research literature spanning three decades. The compound served as proof of concept that glycine-site NMDAR modulation can enhance cognition, but clinical benefit has been modest and inconsistent.

Comparison to dalzanemdor: D-cycloserine modulates NMDAR at the glycine site while dalzanemdor modulates at the oxysterol site; the two compounds address different aspects of NMDAR hypofunction. D-cycloserine has the advantage of an established clinical safety profile and decades of cognitive research, but the clinical benefit for cognition has not supported registration. Dalzanemdor had higher potency and selectivity for NMDAR modulation but also failed to demonstrate clinical cognitive benefit in controlled trials.

12.4 Rapastinel (GLYX-13)

Mechanism: Functional partial agonist at the glycine modulatory site of the NMDAR. Rapastinel is a tetrapeptide (threonine-proline-proline-threonine) that modulates NMDAR function through the glycine site, producing rapid and sustained enhancement of synaptic plasticity without the receptor desensitization or psychotomimetic effects associated with NMDAR antagonists [29, 30].

Development trajectory: Rapastinel was developed by Naurex (later acquired by Allergan) primarily as a rapid-acting antidepressant. Phase 2 studies demonstrated rapid antidepressant effects after single intravenous infusion in treatment-resistant depression, with effects lasting up to 7 days [29]. Rapastinel also enhanced cognition in preclinical models, ameliorating phencyclidine- and ketamine-induced declarative memory deficits in mice and enhancing memory-related task performance in aged animals [30, 31]. In 2019, Allergan announced that rapastinel had failed to meet its primary endpoints in three Phase 3 trials in acute major depressive disorder, and development was discontinued [29].

Novelty: 3/5. The peptide NMDAR modulator concept and glycine-site mechanism are established, but the rapid and sustained antidepressant efficacy was novel at the time of early clinical development.

Effect size: 2/5. Phase 2 antidepressant effect sizes were moderate but not sustained across Phase 3 trials. Preclinical cognitive effect sizes were encouraging but no controlled human cognitive trials were conducted.

Promising potential: 1/5. Development discontinued following Phase 3 failure. No longer in active commercial development. Research-grade rapastinel is available for in vitro and in vivo work.

Side-effect profile: 4/5. Well tolerated in clinical trials; no psychotomimetic effects, no serious adverse events attributed to the compound.

Overall validation: 2/5. Strong preclinical data and encouraging Phase 2 antidepressant results that were not confirmed in Phase 3. No controlled human cognitive efficacy data.

Comparison to dalzanemdor: Both rapastinel and dalzanemdor produced encouraging Phase 2 signals (antidepressant and cognitive, respectively) that were not confirmed in Phase 3 controlled trials. The compounds act at different NMDAR al-

losteric sites (glycine versus oxysterol). The parallel trajectory of promising early signals followed by Phase 3/Phase 2 failure is illustrative of the broader challenge of translating NMDAR modulation into clinical cognitive or psychiatric benefit.

12.5 SGE-301

Mechanism: Synthetic analog of 24(S)-hydroxycholesterol; positive allosteric modulator of the NMDAR at the same oxysterol binding site as dalzanemdor. SGE-301 increases NMDAR channel open probability without direct channel gating, with the same subunit-non-selective profile as dalzanemdor and 24(S)-HC [34, 35].

Development trajectory: SGE-301 was developed by Sage Therapeutics as a pre-clinical research compound and as a potential therapeutic candidate for anti-NMDAR encephalitis. Bhatt et al. (2020) demonstrated that SGE-301 prevented NMDAR dysfunction caused by patient-derived NMDAR antibodies in cultured neurons, providing proof of concept for oxysterol PAM rescue pharmacology in autoimmune NMDAR hypofunction [34]. Bhatt et al. (2019) further characterized SGE-301 as rescuing synaptic transmission and memory in models of NMDAR hypofunction [35]. SGE-301 was optimized for systemic delivery with brain exposures sufficient to modulate NMDAR activity [5, 35]. The compound has not been advanced to clinical trials.

Novelty: 3/5. The oxysterol PAM mechanism is novel in the NMDAR modulator space, but SGE-301 is an earlier-generation compound in the same series that produced dalzanemdor.

Effect size: 2/5. Preclinical rescue pharmacology effects are robust in NMDAR hypofunction models. No human efficacy data.

Promising potential: 2/5. The compound remains in preclinical development. The clinical failure of dalzanemdor (the more advanced compound in the same series) has reduced the translational promise of the oxysterol PAM class for cognitive indications, though the anti-NMDAR encephalitis indication remains theoretically viable.

Side-effect profile: 3/5. Preclinical safety has been reported as adequate. No human safety data.

Overall validation: 2/5. Strong preclinical pharmacology with specific rescue pharmacology applications, but no clinical validation.

Comparison to dalzanemdor: SGE-301 and dalzanemdor share the oxysterol PAM mechanism and act at overlapping NMDAR binding sites. Dalzanemdor was the clinical-stage optimization of the same chemical series, with improved potency and oral pharmacokinetic properties. The clinical failure of dalzanemdor informs the translational risk assessment for SGE-301 and for the oxysterol PAM class more broadly. SGE-301's principal remaining research value is in anti-NMDAR encephalitis rescue pharmacology, a distinct indication from the cognitive impairment indications pursued by dalzanemdor.

12.6 Comparator summary

The five comparators occupy distinct positions in the NMDAR pharmacology landscape. **Memantine** is the only FDA-approved NMDAR-targeting drug, operating through channel blockade rather than potentiation, with modest clinical benefit limited to moderate-to-severe Alzheimer's disease. **NYX-458** represents a structurally novel glycine-site approach to Parkinson's disease cognitive impairment, but its clinical development trajectory has been interrupted by the sponsor's financial difficulties. **D-cycloserine** is the longest-studied NMDAR glycine-site modulator for cognitive enhancement, serving as the historical proof of concept but producing inconsistent clinical benefit. **Rapastinel** demonstrated the Phase 2 to Phase 3 translational failure pattern that dalzanemdor subsequently replicated. **SGE-301** shares dalzanemdor's oxysterol mechanism and provides the preclinical pharmacological foundation for the class.

Dalzanemdor occupies a unique position as the first NMDAR positive allosteric modulator to reach clinical development for cognitive impairment, with a novel oxysterol-derived mechanism distinct from the glycine-site and channel-blocking approaches. The compound demonstrated favorable safety and tolerability across all clinical studies but failed to show cognitive benefit in three controlled Phase 2 trials. The clinical trajectory provides important translational lessons for the NMDAR PAM field: positive open-label cognitive signals in neurodegenerative disease populations do not reliably predict controlled-trial efficacy, and the therapeutic window for NMDAR positive allosteric modulation in human cognitive impairment may be narrower than preclinical models suggest.

13. References

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