

RESEARCH MONOGRAPH . COMPOUND PROFILE

Roluperidone

A cyclic amide derivative with equipotent nanomolar antagonism at sigma-2 and 5-HT2A receptors, developed by Minerva Neurosciences as monotherapy for the negative symptoms of schizophrenia and distinguished from conventional antipsychotics by the absence of dopaminergic receptor binding.

DOCUMENT	KDC-MN-1657
ISSUED	2026-05-22
REVISION	1.0
AUTHOR	Kodi ac bio l abs Research
COMPOUND CLASS	Sigma-2 receptor antagonist and serotonin 5-HT2A receptor antagonist with alpha-1A adrenergic receptor antagonism

ABSTRACT

Roluperidone (MIN-101, formerly MT-210 and CYR-101) is a cyclic amide (isoindolinone) derivative that combines high-affinity antagonism at the sigma-2 receptor (TMEM97; Ki 8.19 nM) and the serotonin 5-HT_{2A} receptor (Ki 7.53 nM) with lower-affinity antagonism at alpha-1A adrenergic receptors (Ki 4.17 nM), while exhibiting essentially no binding at dopamine D₁ through D₅ receptors, muscarinic, cholinergic, or histaminergic receptors. This receptor binding profile distinguishes roluperidone from all marketed antipsychotics and underwrites a pharmacological rationale for addressing the negative symptoms of schizophrenia through nondopaminergic mechanisms. The sigma-2 receptor, identified in 2017 as the transmembrane protein TMEM97, is expressed at high density in cortical and hippocampal neurons and is implicated in calcium signaling, cholesterol homeostasis, autophagy, and the modulation of dopaminergic and glutamatergic neurotransmission. The 5-HT_{2A} antagonist component promotes slow-wave sleep normalization, a deficit that is consistently documented in schizophrenia and that correlates with negative symptom severity. Roluperidone was originally synthesized by Mitsubishi Tanabe Pharma Corporation (designated MT-210), licensed through Cyrenaic Pharmaceuticals (CYR-101), and advanced through clinical development by Minerva Neurosciences (MIN-101). In a Phase 2b randomized, double-blind, placebo-controlled trial of 244 patients with stable schizophrenia and moderate-to-severe negative symptoms (MIN-101C03), roluperidone monotherapy at 32 mg/day and 64 mg/day produced statistically significant improvement on the PANSS negative symptom factor score at 12 weeks (effect sizes 0.45 and

0.58, respectively; both $p < 0.025$). In the subsequent Phase 3 trial (EMERGENT-3, NCT03397134, 513 patients), the 64 mg/day dose reached nominal statistical significance on the primary negative symptom endpoint in the modified intent-to-treat analysis ($p = 0.044$, effect size 0.26), with statistically significant improvements in social functioning on the Personal and Social Performance scale ($p = 0.021$, effect size 0.27) and a negative symptom responder rate of 39% versus 23% on placebo ($p = 0.006$). Network intervention analysis of both trials identified avolition as the directly targeted symptom, with improvements cascading across the broader negative symptom constellation. Pharmacokinetics are characterized by oral bioavailability of 73% to 81%, peak plasma concentration at approximately 3.5 hours, and a plasma elimination half-life of approximately 7 hours after a 64 mg dose, supporting once-daily administration. CYP2D6 is involved in metabolism, and poor or intermediate CYP2D6 metabolizers were excluded from the Phase 3 trial. Tolerability across both trials was notable for the absence of clinically meaningful weight gain, metabolic changes, extrapyramidal symptoms, or prolactin elevation; the principal safety signal was QTc interval prolongation leading to discontinuation of three patients at the 64 mg dose in the Phase 3 trial. Minerva Neurosciences filed a New Drug Application with the U.S. Food and Drug Administration in April 2023. The FDA issued a Complete Response Letter in February 2024, citing insufficient evidence of effectiveness from a single adequate trial, absence of data on concomitant antipsychotic administration, and the need for additional evidence of clinical meaningfulness. The compound remains in development as of the monograph date. This monograph documents the chemistry, dual-receptor pharmacology, pharmacokinetics, preclinical and clinical evidence base, safety

profile, and a comparative assessment of five compounds in the negative symptom treatment space against roluperidone on five competency standards. The compound is investigational and is not approved by any regulatory authority for any indication.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Roluperidone.

Development codes: MT-210 (Mitsubishi Tanabe Pharma Corporation; the original designation under which the compound was synthesized and initially characterized). CYR-101 (Cyrenaic Pharmaceuticals; used in the Phase 2a clinical trial, NCT00861796). MIN-101 (Minerva Neurosciences; the canonical identifier in the Phase 2b and Phase 3 clinical literature and in the NDA submission). FMI (appears in some early database entries).

Chemical Abstracts Service registry numbers: 359625-79-9 (free base); 1937215-88-7 (hydrochloride salt) [1].

Spanish International Nonproprietary Name: Roluperidona.

ChEMBL identifier: ChEMBL4297605. **PubChem compound identifier:** CID 9799284.

1.2 Structural class and chemistry

Roluperidone is a cyclic amide derivative of the isoindolinone structural class. The molecule comprises a 1-isoindolinone (2,3-dihydro-1H-isoindol-1-one) bicyclic core connected through a methylene bridge to the 4-position of a piperidine ring, with the piperidine nitrogen substituted by a 2-oxo-2-(4-fluorophenyl)ethyl group [1, 2].

International Union of Pure and Applied Chemistry name: 2-({1-[2-(4-fluorophenyl)-2-oxoethyl]-4-piperidinyl}methyl)-2,3-dihydro-1H-isoindol-1-one.

Hydrochloride dihydrate (clinical formulation): 1H-Isoindol-1-one, 2-[[1-[2-(4-fluorophenyl)-2-oxoethyl]-4-piperidinyl]methyl]-2,3-dihydro-, hydrochloride, hydrate (1:1:2).

Molecular formula: C₂₂H₂₃FN₂O₂ (free base).

Molecular weight: 366.43 Da (free base) [1, 2].

Canonical**SMILES:**

O=C1N(CC2CCN(CC(C3=CC=C(F)C=C3)=O)CC2)CC4=C1C=CC=C4 [2].

Structural features: The molecule contains a fluorine atom at the para position of the phenyl ring, a ketone carbonyl at the alpha position of the phenyl-piperidine linkage, and a lactam carbonyl within the isoindolinone ring. The piperidine ring is unsubstituted at the 2, 3, 5, and 6 positions and connects to the isoindolinone through a methylene at the 4-position. No stereocenters are present in the molecule; roluperidone does not exhibit optical isomerism [1, 2].

Physical form: The compound is supplied as the hydrochloride dihydrate salt for clinical use and as the free base for research applications. It is formulated as a modified-release oral preparation for the clinical program [3].

1.3 Synthesis

The published chemical literature on the synthesis of roluperidone is limited, as the compound originated from a proprietary medicinal chemistry program at Mitsubishi Tanabe Pharma Corporation. The structure suggests a convergent synthesis involving (a) preparation of the 1-isoindolinone core from phthalic anhydride or a substituted 2-carboxybenzaldehyde through cyclization with an appropriate amine equivalent, (b) preparation of a 4-(aminomethyl)piperidine or equivalent building block, and (c) N-alkylation of the piperidine nitrogen with alpha-bromo-4-fluoroacetophenone or an equivalent electrophilic synthon. Patent literature associated with the MT-210 compound series from Mitsubishi Tanabe covers the preparation and pharmaceutical uses of the isoindolinone-piperidine scaffold [4]. Research-grade synthesis at milligram to gram scale follows standard amide-bond and N-alkylation chemistry amenable to medicinal chemistry laboratories.

2. Abstract

Roluperidone (MIN-101) is a sigma-2 receptor antagonist and 5-HT_{2A} receptor antagonist with no clinically meaningful dopaminergic receptor binding, developed as monotherapy for the negative symptoms of schizophrenia. The compound reached Phase 3 clinical development and NDA submission, received an FDA Complete Response Letter in February 2024, and remains investigational. The dual nondopaminergic mechanism, the clinical evidence for efficacy on negative symptoms and social functioning, and the favorable metabolic and extrapyramidal safety profile distinguish roluperidone from conventional and atypical antipsychotics in the negative symptom treatment space.

3. Discovery and Development History

3.1 Origin

Roluperidone was synthesized by Mitsubishi Tanabe Pharma Corporation as part of a medicinal chemistry program targeting sigma receptor and serotonin receptor ligands, and designated MT-210 [3, 4]. The compound was selected from the isoin-dolinone-piperidine series on the basis of its equipotent nanomolar affinity for sigma-2 and 5-HT_{2A} receptors, its lack of dopaminergic receptor binding, and its favorable preclinical tolerability profile.

3.2 Licensing and early clinical development

Mitsubishi Tanabe licensed the compound to Cyrenaic Pharmaceuticals, a U.S.-based clinical-stage neuroscience company, under which it was designated CYR-101. Cyrenaic conducted the first clinical evaluation of the compound in schizophrenia, a Phase 2a multi-center, double-blind, randomized, placebo-controlled proof-of-concept study (CYR-101C01, NCT00861796) that enrolled patients with schizophrenia and ran from March 2008 to June 2010 [5, 6].

Cyrenaic subsequently merged with Sonkei Pharmaceuticals to form Minerva Neurosciences, Inc. (Burlington, Massachusetts, USA), and the compound was re-designated MIN-101 [3]. Minerva assumed all clinical development responsibilities and advanced the compound through the regulatory process.

3.3 Phase 2b development

Minerva conducted a Phase 2b randomized, double-blind, placebo-controlled trial (MIN-101C03) between May 2015 and December 2015. The trial enrolled 244 patients with stable schizophrenia and moderate-to-severe negative symptoms, randomized 1:1:1 to roluperidone 32 mg/day, 64 mg/day, or placebo for 12 weeks [7]. Both doses achieved statistically significant improvement on the primary endpoint (PANSS negative symptom factor score, pentagonal model) compared to placebo (32 mg: es-

estimated treatment effect -1.54, $p \leq 0.024$, effect size 0.45; 64 mg: estimated treatment effect -1.97, $p \leq 0.0036$, effect size 0.58) [7, 8]. The results were presented at the American College of Neuropsychopharmacology annual meeting in 2017.

3.4 Phase 3 development (EMERGENT-3)

Minerva subsequently conducted the Phase 3 EMERGENT-3 trial (MIN-101C07, NCT03397134, EudraCT 2017-003333-29), a 12-week, randomized, double-blind, placebo-controlled, three-arm trial enrolling 513 patients at 61 sites across Europe, Israel, and the United States between December 2017 and February 2020 [8]. The trial included open-label extension periods of up to 40 weeks. Results were published in Schizophrenia Bulletin in 2022 [8].

3.5 NDA submission and FDA Complete Response Letter

Minerva Neurosciences filed a New Drug Application with the U.S. Food and Drug Administration on April 27, 2023. The FDA accepted the filing on May 8, 2023, and assigned a standard review classification with a Prescription Drug User Fee Act goal date of February 26, 2024 [9].

On February 27, 2024, the FDA issued a Complete Response Letter (CRL) for the roluperidone NDA. The cited deficiencies included: (a) although one study (MIN-101C03) demonstrated statistical significance on the primary efficacy endpoint, it was deemed insufficient on its own to establish substantial evidence of effectiveness; (b) the NDA submission lacked data on concomitant administration with antipsychotic drugs; (c) additional data were needed to establish that the change in negative symptoms with roluperidone treatment was clinically meaningful; and (d) the safety database contained an inadequate number of participants exposed to the proposed 64 mg dose for at least 12 months [9, 10].

3.6 Ongoing development

As of the monograph date (May 2026), Minerva Neurosciences has initiated a study to evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of co-administration of roluperidone and olanzapine in patients with moderate-to-severe negative symptoms of schizophrenia (NCT06107803), addressing the concomi-

tant antipsychotic deficiency cited in the CRL [11]. An investigational new drug application has also been filed for roluperidone in apathy associated with dementia [3].

4. Molecular Pharmacology

4.1 Receptor binding profile

Roluperidone is a multi-target ligand with high equipotent affinities for two principal receptors and a secondary affinity for a third. Radioligand binding studies characterize the compound as follows [8, 12]:

Sigma-2 receptor (TMEM97): K_i 8.19 nmol/L. 5-Hydroxytryptamine type 2A (5-HT_{2A}) receptor: K_i 7.53 nmol/L. Alpha-1A adrenergic receptor: K_i 4.17 nmol/L.

The compound has very low or no measurable affinity for dopamine D1 through D5 receptors ($IC_{50} > 1000$ nmol/L), muscarinic receptors, cholinergic nicotinic receptors, histamine H1 receptors, or the sigma-1 receptor at concentrations relevant to clinical dosing [8, 12]. One metabolite of roluperidone has been reported to show affinity for the histamine H1 receptor, though the identity and clinical significance of this metabolite have not been fully characterized in the peer-reviewed literature [1].

The absence of clinically meaningful dopaminergic binding distinguishes roluperidone from all marketed first-generation and second-generation antipsychotics and is the pharmacological basis for the compound's favorable profile with respect to extrapyramidal symptoms, prolactin elevation, and metabolic syndrome.

4.2 Sigma-2 receptor (TMEM97): identity, function, and roluperidone antagonism

The sigma-2 receptor was identified in 2017 as the transmembrane protein TMEM97 through affinity chromatography with a selective sigma-2 ligand, confirmed by heterologous expression and pharmacological profiling [13, 14]. TMEM97 is structurally distinct from the sigma-1 receptor and is not genetically related to it [14].

TMEM97 resides in the endoplasmic reticulum and lysosomes, where it interacts with the low-density lipoprotein receptor (LDLR) at the plasma membrane to transport apolipoprotein E into neurons and with intracellular Niemann-Pick type C1 protein (NPC1) to regulate LDL cholesterol transport out of lysosomes [15]. Within

the brain, TMEM97 is expressed in the cerebellum, cortex, hippocampus, and substantia nigra, with enrichment in neurons relative to glial cells [15]. At the synaptic level, TMEM97 has been demonstrated by Forster resonance energy transfer to colocalize with amyloid-beta oligomers in synaptic densities [15]. The receptor is implicated in the regulation of autophagy, intracellular trafficking, oxidative stress responses, and calcium signaling [15].

In vivo functional studies confirm that roluperidone acts as an antagonist at the sigma-2 receptor. The selective sigma-2 receptor agonist 1,3-di-o-tolylguanidine (DTG), when injected into the red nucleus of rats, induces neck dystonia through sigma-2 activation. Roluperidone at 1 mg/kg and 3 mg/kg significantly prevented DTG-induced neck dystonia, confirming antagonist activity at the sigma-2 receptor in a validated functional model [8, 12].

The precise mechanism by which sigma-2 receptor antagonism contributes to the amelioration of negative symptoms is not fully elucidated. Proposed pathways include modulation of dopaminergic and glutamatergic neurotransmission downstream of TMEM97 signaling, effects on intraneuronal calcium homeostasis through the ER-lysosomal axis, and modulation of synaptic plasticity through the cholesterol-regulatory and autophagic functions of the receptor [3, 15]. The structural resolution of the sigma-2 receptor co-crystal with ligands, published in Nature by Alon et al. (2021), revealed that the protonated piperidine nitrogen of roluperidone forms a salt bridge with the conserved Asp29 residue and a hydrogen bond with Glu73, positioning the compound within the central binding cavity of the receptor [16].

4.3 5-HT_{2A} receptor antagonism

The 5-HT_{2A} receptor is a Gq-coupled G protein-coupled receptor expressed on cortical pyramidal neurons, thalamic relay neurons, and peripheral cell populations. 5-HT_{2A} receptor activation modulates cortical excitability, thalamocortical information processing, and sleep architecture. 5-HT_{2A} receptor antagonism is a shared pharmacological feature of most second-generation antipsychotics (olanzapine, risperidone, quetiapine, clozapine) and is implicated in the atypicality profile that reduces extrapyramidal symptom liability relative to first-generation dopamine-blocking agents.

Roluperidone antagonizes the 5-HT_{2A} receptor with high affinity (K_i 7.53 nmol/L). The functional effect was confirmed in the head-twitch response assay, in which the anhydrous form of roluperidone at 0.27 mg/kg administered orally to male Wistar rats significantly reduced the number of head-twitches induced by 5-hydroxytryptophan, consistent with 5-HT_{2A} receptor antagonism [8, 12].

The therapeutic relevance of 5-HT_{2A} antagonism in negative symptoms operates principally through sleep architecture. Slow-wave sleep (stages N3) is consistently disrupted in patients with schizophrenia, and the severity of sleep disruption correlates with negative symptom burden. 5-HT_{2A} receptor antagonism promotes slow-wave sleep normalization, providing a potential mechanistic link between the receptor pharmacology and the clinical effect on negative symptoms [3, 12].

4.4 Alpha-1A adrenergic receptor antagonism

Roluperidone binds the alpha-1A adrenergic receptor with a K_i of 4.17 nmol/L, a higher affinity than its binding at either the sigma-2 or 5-HT_{2A} receptor [8, 12]. The alpha-1A adrenergic receptor is expressed on central and peripheral neurons and on vascular smooth muscle. Antagonism at central alpha-1A adrenergic receptors, in combination with sigma-2 antagonism, has been proposed to increase intraneuronal calcium levels through disinhibition of calcium signaling pathways, potentially improving memory and cognitive function [3]. The clinical contribution of the alpha-1A component to the overall pharmacological effect is not independently established in human studies.

4.5 Downstream neurobiological effects

Preclinical investigations report that roluperidone treatment produces effects on brain-derived neurotrophic factor (BDNF) expression, which is associated with neurogenesis, neuroplasticity, neuroprotection, synapse regulation, and learning and memory [3]. Network intervention analysis of the Phase 2b and Phase 3 clinical data indicates that roluperidone at the efficacious 64 mg/day dose exerts a direct effect on avolition, the motivational deficit that is a core component of the negative symptom construct, and that improvement in avolition cascades across the broader negative symptom constellation including blunted affect, alogia, and asociality [17].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Roluperidone is administered orally as a modified-release formulation. After a single 64 mg oral dose in healthy subjects, roluperidone was absorbed with a median time to peak plasma concentration (T_{max}) of 3.5 hours, a maximum plasma concentration (C_{max}) of 32.1 ng/mL, and an area under the plasma concentration-time curve from zero to infinity (AUC_{inf}) of 312 ng per hour per mL [12]. The fraction absorbed ranged from 73% to 81% [12].

The presence of food slowed the rate of absorption of roluperidone but produced no significant differences in total exposure between fed and fasted states [12]. The absence of a clinically meaningful food effect supports administration without regard to meals.

5.2 Distribution

The apparent volume of distribution (V_d/F) after oral administration is approximately 1500 L, indicating extensive tissue distribution consistent with a lipophilic compound with substantial central nervous system penetration [12]. Protein binding data have not been published in the peer-reviewed literature as of the monograph date.

5.3 Metabolism

The apparent oral clearance (CL/F) is 152 L/hr [12]. Metabolism involves cytochrome P450 2D6 (CYP2D6), as established by a dedicated Phase 1 clinical pharmacology study (NCT03072056) that compared the pharmacokinetics of roluperidone and its metabolites in healthy subjects stratified by CYP2D6 genotype as poor versus extensive metabolizers [19]. The identity and pharmacological activity of the principal metabolites have not been fully reported in the peer-reviewed literature; one metabolite has been reported to bind the histamine H1 receptor [1].

The clinical significance of the CYP2D6 polymorphism for roluperidone exposure was sufficient to warrant exclusion of CYP2D6 poor and intermediate metabolizers from the Phase 3 trial (EMERGENT-3), a protocol-specified criterion [8]. This exclusion suggests that poor metabolizer status produces substantially elevated roluperidone exposure, though the magnitude of the pharmacokinetic difference has not been reported in a peer-reviewed publication.

5.4 Elimination

The plasma elimination half-life after a 64 mg oral dose is approximately 7 hours in CYP2D6 extensive metabolizers [12]. The half-life is consistent with once-daily dosing, and pharmacokinetic parameters observed in patient populations were comparable to those in healthy subjects [12].

5.5 Special populations

No clinically relevant differences in the pharmacokinetics of roluperidone were observed between male and female subjects in the Phase 1 program [12]. Detailed pharmacokinetic characterization in renal impairment, hepatic impairment, and elderly populations has not been published. Pediatric pharmacokinetics have not been studied.

5.6 Drug-drug interaction potential

Formal drug-drug interaction studies with CYP2D6 inhibitors and other co-mediations have not been reported in the peer-reviewed literature. Given the CYP2D6 involvement in metabolism, co-administration with strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine) would be expected to increase roluperidone exposure, analogous to the CYP2D6-dependent polymorphic pharmacokinetics observed for other psychiatric medications metabolized by CYP2D6. The ongoing study of roluperidone co-administered with olanzapine (NCT06107803) will provide additional pharmacokinetic interaction data [11].

6. Preclinical Pharmacology

6.1 In vivo sigma-2 receptor antagonism

The functional antagonist activity of roluperidone at the sigma-2 receptor was established using the DTG-induced neck dystonia model in rats. Injection of the sigma-2 agonist 1,3-di-o-tolylguanidine (DTG) into the red nucleus produces dystonic neck posturing through sigma-2 receptor activation. Systemic administration of roluperidone at 1 mg/kg and 3 mg/kg significantly prevented DTG-induced neck dystonia, confirming antagonist function at the sigma-2 receptor in vivo [8, 12]. The dose-response relationship across these two doses supports the interpretation of receptor occupancy-dependent antagonism at doses that translate to clinical exposures.

6.2 In vivo 5-HT_{2A} receptor antagonism

The 5-HT_{2A} antagonist activity was confirmed using the head-twitch response (HTR) assay, a validated behavioral model of central 5-HT_{2A} receptor function. Administration of 5-hydroxytryptophan to rodents produces head-twitch responses through serotonergic pathways that are selectively blocked by 5-HT_{2A} antagonists. The anhydrous form of roluperidone, administered orally at 0.27 mg/kg to male Wistar rats, significantly reduced the number of head-twitches, demonstrating 5-HT_{2A} receptor antagonism at a low oral dose [8, 12].

6.3 Absence of dopaminergic effects

A critical feature of roluperidone's preclinical pharmacology is the absence of dopaminergic receptor activity. In standard receptor binding panels, roluperidone showed IC₅₀ values exceeding 1000 nmol/L at all dopamine receptor subtypes (D1 through D5), with no measurable agonist or antagonist activity at concentrations up to 100-fold above the sigma-2 and 5-HT_{2A} binding affinities [8, 12]. This absence of dopaminergic binding predicts the clinical observations of no extrapyramidal motor effects, no prolactin elevation, and no metabolic dysregulation. The selectivity

is notable in the context of a compound intended for schizophrenia, where virtually all approved pharmacotherapies exert their principal effects through dopamine D2 receptor modulation.

6.4 Neurotrophic and neuroplasticity effects

Preclinical studies have reported that roluperidone treatment produces effects on brain-derived neurotrophic factor (BDNF) expression [3]. BDNF is a neurotrophin involved in neurogenesis, synaptic plasticity, neuroprotection, and memory consolidation. Sigma-2 receptor modulation has been independently linked to BDNF signaling in neuronal cell models, providing a plausible molecular pathway connecting the receptor pharmacology to neuroplastic outcomes [15]. The specific experimental systems, doses, species, and magnitude of BDNF modulation produced by roluperidone have not been fully detailed in the peer-reviewed literature; the available characterization is principally from the sponsor's preclinical summary.

6.5 Translational pharmacology

The sigma-2 receptor crystal structure resolved by Alon et al. (2021) provides a structural basis for understanding the binding mode of roluperidone at its primary target [16]. The co-crystal structure reveals that the protonated piperidine nitrogen of roluperidone forms a salt bridge with the conserved Asp29 residue and a hydrogen bond with Glu73 within the central binding cavity of the TMEM97 receptor [12, 16]. This structural information facilitates structure-activity relationship analysis for next-generation sigma-2 ligands and provides a molecular rationale for the high-affinity binding observed in radioligand displacement assays.

6.6 Gaps in the preclinical evidence

The absence of formal behavioral pharmacology studies in validated animal models of negative symptoms (e.g., social interaction deficits in isolation-reared rodents, anhedonia-like behaviors in sucrose preference assays, cognitive inflexibility in attentional set-shifting paradigms) represents a notable gap in the preclinical literature for roluperidone. Standard preclinical development programs for negative symptom compounds typically include efficacy demonstrations in social withdrawal models and motivational deficit paradigms. For roluperidone, the preclinical evidence is limited to receptor-binding and functional-antagonism studies; the translation to negative symptom efficacy was established directly in clinical trials

rather than through conventional preclinical efficacy modeling. Investigators considering roluperidone for preclinical research should note this gap when designing translational pharmacology studies.

7. Clinical Evidence Base

The following clinical evidence is presented for research context. Roluperidone is an investigational compound that is not approved by any regulatory authority for any indication. All clinical findings are from controlled research settings.

7.1 Phase 2a (CYR-101C01)

The earliest clinical evaluation of roluperidone in schizophrenia was a multi-center, inpatient and ambulatory, Phase 2, double-blind, randomized, placebo-controlled proof-of-concept study (CYR-101C01, NCT00861796) conducted under the Cyrenaic Pharmaceuticals designation between March 2008 and June 2010 [5, 6]. The study included patients with schizophrenia and evaluated an early formulation of the compound. Detailed results of this study have not been published in the peer-reviewed literature, and it is referenced principally as a historical milestone in the development program.

7.2 Phase 2b (MIN-101C03)

The pivotal Phase 2b trial (MIN-101C03) was a multinational, 12-week, randomized, double-blind, placebo-controlled, three-arm, parallel-group study conducted between May 2015 and December 2015 [7, 8]. The trial enrolled 244 patients diagnosed with schizophrenia who were symptomatically stable for at least 3 months prior to enrollment and had scores of 20 or greater on the PANSS negative symptoms subscale (three-factor model). Patients were randomized 1:1:1 to roluperidone 32 mg/day, roluperidone 64 mg/day, or placebo, administered as monotherapy.

The primary endpoint was the PANSS negative symptom factor score based on the pentagonal structure model. PANSS negative factor scores improved significantly with roluperidone beginning at Week 2, and by Week 12, both roluperidone treatment groups showed statistically significant improvements compared to placebo: the 32 mg group produced an estimated treatment effect of -1.54 ($p \leq 0.024$, effect size 0.45) and the 64 mg group produced an estimated treatment effect of -1.97 ($p \leq 0.0036$, effect size 0.58) [7, 8].

No weight gain or clinically significant changes in vital signs, prolactin levels, routine laboratory values, metabolic indices, or extrapyramidal symptom scores were observed in any treatment group [7]. One patient in the 64 mg group was discontinued for QT prolongation and one for syncope [7].

A 24-week open-label extension followed the double-blind phase, with 142 of the 244 randomized patients entering the extension. During the open-label period, continued improvements in negative symptoms were observed, and the rate of symptomatic worsening requiring antipsychotic treatment was 9.1% [20].

7.3 Phase 2b secondary analyses

7.3.1 Cognitive effects

Keefe et al. (2018) reported a post-hoc analysis of cognitive outcomes from the Phase 2b trial using the Brief Assessment of Cognition in Schizophrenia (BACS) battery [21]. In the 32 mg group compared to placebo, significant improvements were observed on the BACS token motor test ($p = 0.04$), verbal fluency ($p = 0.01$), and composite z score ($p = 0.05$). At Week 12 in the 64 mg group, improvement in the PANSS negative factor showed significant correlations with improvements in the BACS composite score ($r = -0.408$, $p = 0.002$), Trail Making Test ($r = -0.394$, $p = 0.003$), and verbal memory ($r = -0.322$, $p = 0.017$) [21]. The correlation between negative symptom improvement and cognitive improvement suggests either a shared mechanism or a functional relationship between negative symptom amelioration and cognitive performance.

7.3.2 Negative symptom dimensions

Harvey et al. (2020) analyzed the effects of roluperidone on the two recognized dimensions of negative symptoms, reduced emotional experience (avolition, anhedonia) and reduced emotional expression (blunted affect, alogia), using the Phase 2b data [22]. Both roluperidone doses produced significant improvements on both dimensions: reduced experience (32 mg: $p \leq 0.006$; 64 mg: $p \leq 0.001$) and reduced expression (32 mg: $p \leq 0.003$; 64 mg: $p \leq 0.001$) [22]. The breadth of effect across both negative symptom dimensions is notable, as some interventions (e.g., cariprazine) show differential effects on the two dimensions.

7.4 Phase 3 (EMERGENT-3, MIN-101C07)

The Phase 3 trial (EMERGENT-3, NCT03397134, EudraCT 2017-003333-29) was a 12-week, randomized, double-blind, placebo-controlled, three-arm, parallel-group study that enrolled 513 patients with schizophrenia and moderate-to-severe negative symptoms at 61 sites in Europe, Israel, and the United States between December 2017 and February 2020 [8].

Inclusion criteria: DSM-5 diagnosis of schizophrenia for at least one year; negative symptoms for at least 6 months; PANSS negative symptoms subscale score greater than 20 with no more than 3-point change between screening and baseline; stable positive symptoms with individual PANSS positive items scores of 4 or below; Clinical Global Impression-Severity score consistent with moderate illness [8].

Exclusion criteria: Calgary Depression Scale for Schizophrenia total score greater than 6; moderate or greater akathisia on the Barnes Akathisia Rating Scale; body mass index of 35 kg/m² or greater; personal or familial history of long QT syndrome; QTcF greater than 430 ms for males or greater than 450 ms for females; CYP2D6 poor or intermediate metabolizer status; positive urine drug screen or substance abuse history; comorbid Axis I diagnosis; significant suicide risk [8].

Randomization: Patients were randomized 1:1:1 to roluperidone 32 mg/day (n = 170), roluperidone 64 mg/day (n = 171), or placebo (n = 172), stratified by region (United States versus all other countries). All psychotropic medications were discontinued at least 2 days before randomization. Roluperidone was administered as monotherapy throughout the 12-week double-blind period [8].

Demographics: Mean age 41 years (SD 9.1); 61% male; 88% White, 11% Black or African American; mean BMI 25.7 kg/m²; 16% from the United States, 84% from other countries. Baseline PANSS NSFS was approximately 25 (SD 3.2), PANSS total approximately 79 (SD 10.8), and PSP total approximately 53 (SD 11.2) across groups [8].

Primary endpoint (PANSS Marder Negative Symptom Factor Score, NSFS): In the intent-to-treat analysis, roluperidone 64 mg produced a least-squares mean change from baseline of -4.3 (SEM 0.34) versus -3.5 (SEM 0.34) for placebo, a difference that marginally missed statistical significance (p = 0.064, effect size 0.21). In the modified intent-to-treat analysis, the 64 mg dose reached nominal statistical significance

(least-squares mean change -4.5, SEM 0.35, versus -3.5, SEM 0.35; difference -0.96, 95% CI -1.89 to -0.03; $p = 0.044$, effect size 0.26). The 32 mg dose did not reach statistical significance on the primary endpoint ($p = 0.259$) [8].

Key secondary endpoint (Personal and Social Performance scale, PSP): In the ITT analysis, roluperidone 64 mg produced a mean change of +6.1 versus +3.9 for placebo (least-squares mean difference 2.20, 95% CI 0.33 to 4.06; $p = 0.021$, effect size 0.27). In the mITT analysis, the difference was 2.40 (95% CI 0.44 to 4.35; $p = 0.017$, effect size 0.29) [8].

Responder analyses: A 20% or greater reduction in NSFS was achieved by 39% of patients on roluperidone 64 mg versus 23% on placebo ($p = 0.006$). A 20% or greater reduction in PANSS total score was achieved by 20% on roluperidone 64 mg versus 9% on placebo ($p = 0.021$). A 7-point or greater improvement on the PSP was achieved by 41% on roluperidone 64 mg versus 29% on placebo ($p = 0.032$) [8].

Additional secondary endpoints: PANSS negative symptoms subscore: 64 mg -4.7 versus -3.8, $p = 0.046$, effect size 0.23. NSFS emotional experience subscore (avolition-related items): 64 mg -1.8 versus -1.3, $p = 0.020$, effect size 0.28. CGI-Severity: 64 mg -0.5 versus -0.3, $p = 0.073$ (not significant). Calgary Depression Scale for Schizophrenia: no significant differences. Verbal fluency test: no significant differences [8].

Completion rates: 76% placebo, 72% roluperidone 32 mg, 74% roluperidone 64 mg completed the 12-week double-blind period [8].

7.5 Long-term extension data

Rabinowitz et al. (2023) reported the protocol-specified analysis of open-label extension periods from both randomized controlled trials [20]. Following the 12-week double-blind phase, 142 of 244 patients from the Phase 2b trial entered a 24-week open-label extension, and 341 of 513 patients from the Phase 3 trial entered a 40-week open-label extension, receiving roluperidone 32 mg/day or 64 mg/day as monotherapy.

During the open-label extensions, continued improvements in negative symptoms and PSP scores were observed. The overall rate of psychotic exacerbation or hospitalization was below 12%, and antipsychotic medication was administered to 9.1% of patients in the Phase 2b extension and 8% in the Phase 3 extension [20]. Roluperidone was well tolerated during long-term administration with no mean-

ingful changes in vital signs, routine laboratory values, weight gain, metabolic indices, or extrapyramidal symptoms [20]. The low rate of psychotic worsening during monotherapy, in a population that had discontinued all antipsychotic medications, is a notable finding given the high relapse rates typically observed after antipsychotic discontinuation in schizophrenia.

7.6 Network intervention analysis

James et al. (2024) applied network intervention analysis to the Phase 3 trial data (n = 496) to identify the specific negative symptom items directly affected by roluperidone treatment [17]. The analysis demonstrated that the efficacious 64 mg/day dose of roluperidone had a direct effect on avolition, suggesting that changes in avolition drive treatment effects across the entire negative symptom constellation. This finding replicated the network analysis results from the Phase 2b trial, indicating reproducibility of the avolition-targeting mechanism across independent patient populations [17].

8. Sourcing and Quality Verification

Roluperidone is an investigational compound that has not been approved for any indication by any regulatory authority. It is not available as a pharmaceutical-grade registered medicine. The compound is supplied for research purposes by multiple chemical and pharmaceutical research suppliers.

Research-grade roluperidone is available from chemical suppliers including MedChemExpress, Selleckchem, Tocris, Cayman Chemical, MedKoo Biosciences, and TargetMol, typically as the free base at purity greater than 98% by HPLC [1]. Supply is in milligram to gram quantities.

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

- High-performance liquid chromatography (HPLC) with ultraviolet detection for area-percent purity, targeting greater than 98% purity
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+$ of 367.18 for the protonated free base)
- Nuclear magnetic resonance spectroscopy (1H NMR and ^{13}C NMR) for structural verification
- Liquid chromatography-mass spectrometry for metabolite or degradation product identification
- Karl Fischer titration or thermogravimetric analysis for residual water content, particularly for the hydrochloride dihydrate salt form

The research-grade market for roluperidone is relatively recent and smaller in scale than that for registered compounds. Independent third-party analytical verification of vendor certificates of analysis is recommended for any investigation where dose-response precision or pharmacological specificity is important.

9. Reconstitution and Handling

Roluperidone is supplied as a solid (free base or hydrochloride salt) and is reconstituted as needed for research applications. The following handling considerations apply:

Solubility: The free base is expected to be soluble in dimethyl sulfoxide (DMSO) at concentrations suitable for in vitro pharmacology (typically 10 to 50 mM stock solutions). Aqueous solubility of the free base is limited; the hydrochloride salt form provides improved aqueous solubility.

Storage: Solid material should be stored at -20 degrees Celsius for long-term stability, protected from moisture. Stock solutions in DMSO should be stored at -20 degrees Celsius in sealed, desiccated containers and used within 3 months of preparation.

Working solutions: For in vitro assays, serial dilutions from DMSO stock into assay buffer should maintain final DMSO concentration below 0.1% to 0.5% (depending on the assay system sensitivity to DMSO). For in vivo research, the hydrochloride salt dissolved in physiological saline or suspended in standard oral gavage vehicles (0.5% methylcellulose, 0.1% Tween-80 in water) is appropriate.

Stability: Detailed stability data under various storage conditions have not been published in the peer-reviewed literature. Standard pharmaceutical chemistry principles for isoindolinone derivatives predict stability under refrigerated, dry conditions for at least 12 months and susceptibility to hydrolysis under prolonged exposure to heat, strong acid, or strong base.

Light protection: Photostability data are not published. Reasonable practice is to protect stock solutions and solid material from prolonged light exposure.

10. Stack Interaction Considerations

Roluperidone interacts with co-administered compounds through its CYP2D6-mediated metabolism and through its multi-receptor pharmacology. Investigators conducting research with roluperidone in combination with other agents should consider the following interaction categories:

CYP2D6 inhibitors: Strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine, terbinafine) are expected to substantially elevate roluperidone exposure based on the CYP2D6 metabolizer phenotype exclusion in the Phase 3 trial. Co-administration with strong CYP2D6 inhibitors should be approached with caution. Moderate inhibitors (sertraline, duloxetine) may produce smaller but measurable effects.

CYP2D6 inducers: Inducers of CYP2D6 (rifampin as a broad CYP inducer) could reduce roluperidone exposure and attenuate pharmacological effects.

Antipsychotic medications: The Phase 2b and Phase 3 clinical programs administered roluperidone as monotherapy with all antipsychotic medications discontinued. The ongoing olanzapine co-administration study (NCT06107803) is designed to evaluate pharmacokinetic and pharmacodynamic interactions with a representative second-generation antipsychotic [11]. Until these data are available, the interaction profile with concurrent antipsychotics is uncharacterized in a controlled setting.

Other 5-HT_{2A} antagonists: Co-administration with other 5-HT_{2A} antagonists or inverse agonists (pimavanserin, lumateperone, low-dose quetiapine) produces pharmacologically redundant 5-HT_{2A} receptor occupancy. The combination has not been studied and would not be expected to produce additional 5-HT_{2A}-mediated benefit at fully occupying doses of either agent.

QT-prolonging agents: Roluperidone was associated with QTc prolongation leading to discontinuation in four patients across the clinical program (three at 64 mg in the Phase 3 trial) [8]. Co-administration with other QT-prolonging agents (certain antipsychotics, methadone, fluoroquinolones, citalopram, class Ia or III antiarrhythmics) increases the risk of clinically significant QT prolongation and should be managed with ECG monitoring.

CNS depressants: The alpha-1A adrenergic antagonism (K_i 4.17 nM) predicts potential additive effects with other CNS depressants, including sedation and orthostatic hypotension. Combination with benzodiazepines, opioids, or sedating antihistamines should be approached with appropriate monitoring.

11. Adverse Events and Safety Signal

11.1 Common adverse events in the Phase 3 trial

Treatment-emergent adverse events (TEAEs) were experienced by 37% of patients receiving roluperidone 64 mg, 42% receiving roluperidone 32 mg, and 33% receiving placebo in the Phase 3 trial [8]. The most common TEAEs across all treatment groups included:

- Insomnia: approximately 10% in both roluperidone and placebo groups
- Worsening of schizophrenia: 8.0% roluperidone versus 3.0% placebo
- Headache: approximately 5.0% in both groups
- Anxiety: approximately 4.0% roluperidone versus 2.0% placebo
- Agitation: approximately 3.0% roluperidone versus 2.0% placebo [8]

The majority of TEAEs were mild to moderate in severity, with severe TEAEs reported in 17 patients (3%) overall [8].

11.2 Metabolic and extrapyramidal safety

A distinguishing feature of the roluperidone safety profile is the absence of clinically meaningful metabolic and extrapyramidal effects. In the Phase 3 trial [8]:

- **Weight change:** Placebo -0.2 kg (SD 2.97), roluperidone 32 mg 0.0 kg (SD 3.96), roluperidone 64 mg +0.1 kg (SD 2.87). No clinically significant weight gain in any group.
- **Waist circumference:** No meaningful changes across groups.
- **Prolactin:** No differences in prolactin plasma levels between treatment groups and placebo.
- **Extrapyramidal symptoms:** No changes on the Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), or Simpson-Angus Scale (SAS), all of which had baseline scores near zero [8].
- **Suicidality:** No changes on the Sheehan Suicidality Tracking Scale [8].

This profile is consistent with the absence of dopaminergic, muscarinic, and histaminergic receptor binding and is maintained during long-term open-label administration of up to 40 weeks [20].

11.3 Cardiac safety

Four patients in the roluperidone treatment groups across the Phase 3 trial were discontinued due to cardiac disorders or ECG abnormalities: three patients in the 64 mg group for electrocardiogram QT prolongation, and one patient in the 32 mg group for left ventricular dysfunction and T-wave inversion (both events in the same patient). No patients in the placebo group were discontinued for cardiac reasons [8].

The QTc signal, while numerically small in incidence, was sufficient for the FDA to include it among the safety database considerations in the Complete Response Letter. The exclusion of patients with familial or personal history of long QT syndrome and with baseline QTcF above sex-specific thresholds from the Phase 3 trial limits the generalizability of the cardiac safety data to unscreened populations [8].

11.4 Serious adverse events and deaths

Serious adverse events occurred in 5% of all patients: 3% in the placebo group and 6% in the combined roluperidone groups [8]. Two deaths occurred during the Phase 3 trial, both in the roluperidone 32 mg group: one patient died by suicide, and one died from gastrointestinal bleeding six days after withdrawing consent and discontinuing the trial. Neither death was considered by the investigator to be related to study treatment [8].

11.5 Discontinuation due to adverse events

Overall, 5% of patients in the placebo group, 11% in the roluperidone 32 mg group, and 9% in the roluperidone 64 mg group reported TEAEs that led to study drug discontinuation. Relapse (worsening of schizophrenia symptoms) was the most frequent reason for discontinuation, with the highest incidence in the 32 mg group (11%) and the lowest in the placebo group (5%) [8].

11.6 Long-term safety

During open-label extension periods of 24 weeks (Phase 2b) and 40 weeks (Phase 3), no clinically significant changes were observed in vital signs, routine laboratory values, weight, metabolic indices, or extrapyramidal symptom scores [20]. The rate of psychotic exacerbation requiring discontinuation of roluperidone and treatment with an antipsychotic was below 10% over the extension period [20].

12. Comparative Assessment

This section presents a structured comparative assessment of five compounds in the negative symptom treatment space against roluperidone, evaluated on five competency standards: novelty of mechanism, effect size on negative symptom endpoints, promising potential (current clinical trajectory), side-effect profile, and overall validation of the clinical evidence. The comparators were selected as the principal compounds with substantive clinical evidence for the treatment of negative symptoms of schizophrenia, with priority on those with Phase 2 or Phase 3 data and on those that share roluperidone's positioning as a negative-symptom-targeted intervention.

12.1 Cariprazine

Mechanism: Dopamine D3-preferring D3/D2 receptor partial agonist and serotonin 5-HT1A receptor partial agonist. The preferential D3 partial agonism, with approximately 6- to 8-fold higher affinity for D3 than D2, is the proposed mechanistic basis for efficacy on negative symptoms, as D3 receptor signaling in the mesolimbic and mesocortical pathways is implicated in motivational deficits [23].

Development trajectory: Cariprazine (RGH-188, Gedeon Richter/AbbVie) is FDA-approved for the treatment of schizophrenia (2015) and for the treatment of bipolar I disorder (manic and mixed episodes and bipolar depression). While not specifically approved for negative symptoms, a prospectively designed Phase 3b trial evaluated cariprazine specifically for predominant negative symptoms of schizophrenia.

Clinical outcome: Nemeth et al. (2017) reported a 26-week, randomized, double-blind Phase 3b trial in 461 patients comparing cariprazine (3 to 6 mg/day, mean 4.2 mg) with risperidone (3 to 6 mg/day, mean 3.8 mg) in patients with predominant negative symptoms [23]. The primary endpoint was the PANSS factor score for negative symptoms (PANSS-FSNS). Cariprazine produced significantly greater improvement than risperidone (PANSS-FSNS change: -8.90 versus -7.44, least-squares mean difference -1.46, 95% CI -2.39 to -0.53, $p = 0.0022$, effect size 0.31) [23].

Novelty: 3/5. The D3 partial agonist mechanism is partially novel within the antipsychotic class but retains D2 binding and the associated dopaminergic pharmacology profile.

Effect size: 3/5. Effect size of 0.31 versus an active comparator (risperidone) is clinically meaningful but modest. Direct comparison with placebo-controlled negative symptom trials is confounded by the active-comparator design.

Promising potential: 4/5. The compound is FDA-approved and commercially available. Negative symptom benefit is supported by a dedicated prospective trial, though without a specific negative symptom indication approval.

Side-effect profile: 3/5. TEAEs occurred in 54% (cariprazine) versus 57% (risperidone). Cariprazine retains dopaminergic pharmacology and is associated with akathisia, extrapyramidal symptoms, and weight gain, though at lower rates than some second-generation antipsychotics [23].

Overall validation: 4/5. Cariprazine has the strongest evidence base of any currently approved antipsychotic for negative symptom efficacy, supported by a prospectively designed active-comparator trial in a negative-symptom-selected population.

Comparison to roluperidone: Cariprazine operates through a fundamentally different mechanism (dopaminergic partial agonism versus nondopaminergic sigma-2/5-HT2A antagonism). Roluperidone's Phase 2b effect sizes (0.45 and 0.58 versus placebo) are numerically larger than cariprazine's effect size versus risperidone (0.31), though direct comparison is complicated by different comparators (placebo versus active) and different trial designs. Roluperidone's metabolic and EPS-free safety profile is a differentiating advantage; cariprazine's approved status and availability are practical advantages.

12.2 Pimavanserin

Mechanism: Selective serotonin 5-HT2A inverse agonist without dopaminergic, adrenergic, histaminergic, or muscarinic receptor binding. FDA-approved for Parkinson's disease psychosis (2016) [24].

Development trajectory: Acadia Pharmaceuticals conducted the ADVANCE trial, a Phase 2, 26-week, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin in 403 patients with schizophrenia and predominant negative

symptoms on stable background antipsychotic therapy [24, 25].

Clinical outcome: The primary endpoint (NSA-16 total score) was met: pimavanserin at the 34 mg dose produced a least-squares mean change of -11.6, compared to -8.5 for placebo (difference -3.1, $p = 0.0065$, Cohen's $d = 0.339$). The 20 mg dose did not separate from placebo [25]. Secondary endpoints including the PANSS negative symptoms subscore (unadjusted $p = 0.047$) and PANSS Marder Negative Factor score (unadjusted $p = 0.036$) supported the primary result [25].

Novelty: 2/5. The 5-HT_{2A} inverse agonist mechanism is shared with the 5-HT_{2A} antagonist component of roluperidone and is a known pharmacological feature of multiple atypical antipsychotics. Selectivity is the novel aspect.

Effect size: 3/5. Cohen's d of 0.339 at 34 mg represents a small-to-moderate effect, comparable to roluperidone's Phase 3 effect size (0.26 mITT) but smaller than roluperidone's Phase 2b effect sizes.

Promising potential: 3/5. Pimavanserin is being developed as adjunctive therapy (not monotherapy) for negative symptoms. A Phase 3 ENHANCE study has been completed. The compound is approved for a different indication, providing commercial and safety database advantages.

Side-effect profile: 4/5. TEAEs were comparable to placebo (39.9% versus 36.4%). No clinically significant metabolic, EPS, or weight effects. The favorable profile is consistent with the selective 5-HT_{2A} mechanism [25].

Overall validation: 3/5. Phase 2 evidence is positive for the 34 mg dose. The adjunctive approach (pimavanserin added to ongoing antipsychotic) addresses a different clinical question than roluperidone monotherapy and may have more immediate regulatory feasibility given the FDA's concern about roluperidone's lack of concomitant antipsychotic data.

Comparison to roluperidone: Pimavanserin shares the 5-HT_{2A} antagonist mechanism with roluperidone but lacks the sigma-2 and alpha-1A components. The adjunctive design avoids the antipsychotic withdrawal challenge that complicates roluperidone's monotherapy program. Roluperidone's dual mechanism provides a broader pharmacological rationale; pimavanserin's selectivity provides cleaner mechanistic attribution.

12.3 Ulotaront (SEP-363856)

Mechanism: Trace amine-associated receptor 1 (TAAR1) agonist and serotonin 5-HT_{1A} receptor partial agonist. No binding at D₂ dopamine receptors or 5-HT_{2A} serotonin receptors. The compound represents a fundamentally novel antipsychotic mechanism that does not involve dopamine D₂ receptor blockade [26].

Development trajectory: Sunovion (now Sumitomo Pharma) advanced ulotaront through a Phase 2 trial in acute schizophrenia (Koblan et al., New England Journal of Medicine, 2020) [26] and received FDA Breakthrough Therapy Designation. Two Phase 3 trials (DIAMOND-1 and DIAMOND-2) were conducted.

Clinical outcome: The Phase 2 trial randomized 245 patients with acute exacerbation of schizophrenia to ulotaront (50 to 75 mg/day, n = 120) or placebo (n = 125) for 4 weeks. Ulotaront significantly improved the PANSS total score (least-squares mean change -17.2 versus -9.7, difference -7.5, effect size d = 0.45, p = 0.001) [26]. Post-hoc analyses suggested benefit on negative symptoms. A 26-week open-label extension demonstrated sustained improvements with mean PANSS total change of -22.6 (effect size 1.46) [27]. In July 2023, Sumitomo announced that both Phase 3 trials (DIAMOND-1, 435 subjects; DIAMOND-2, 464 subjects) failed to meet primary endpoints, with ulotaront not superior to placebo on PANSS total score [28].

Novelty: 5/5. The TAAR1 agonist mechanism is the most novel in the current schizophrenia pipeline and represents a genuine departure from dopaminergic pharmacology.

Effect size: 3/5. Phase 2 effect size of 0.45 on PANSS total was promising. Phase 3 failure suggests the effect size is not robust across larger, more diverse patient populations.

Promising potential: 2/5. The Phase 3 failures have substantially diminished the near-term development trajectory. The compound retains investigational interest and additional trials are being considered, but the clinical momentum has been significantly set back.

Side-effect profile: 5/5. No extrapyramidal effects, no metabolic effects, no prolactin elevation, no weight gain. The safety profile is the most favorable of any antipsychotic candidate in development [26, 27].

Overall validation: 2/5. Phase 2 data are positive but Phase 3 replication has failed. The compound represents a validated concept (TAAR1 agonism) with an unresolved clinical development problem.

Comparison to roluperidone: Both roluperidone and ulotaront represent non-dopaminergic approaches to schizophrenia, but through entirely different mechanisms. Ulotaront's Phase 3 failure on the broad PANSS total endpoint does not directly predict failure on negative symptom endpoints; conversely, roluperidone's Phase 3 marginal significance on negative symptoms does not predict failure on the PANSS total. The two compounds illustrate the challenge of demonstrating novel-mechanism antipsychotic efficacy in adequately powered, placebo-controlled trials.

12.4 Lumateperone (ITI-007)

Mechanism: Simultaneous modulation of serotonin, dopamine, and glutamate neurotransmission. High-affinity 5-HT_{2A} antagonism (60-fold selectivity over D₂), low D₂ occupancy (approximately 40% at clinical doses), and indirect glutamate modulation through downstream effects on NMDA and AMPA receptor signaling [29].

Development trajectory: Intra-Cellular Therapies developed lumateperone (Caplyta), which received FDA approval for schizophrenia (2019) at 42 mg once daily and for bipolar depression (2021).

Clinical outcome: Phase 3 trials (ITI-007-005 and ITI-007-301) demonstrated statistically significant superiority over placebo on PANSS total score at Day 28 [29]. Subgroup analyses demonstrated greater improvements in patients with prominent negative symptoms on the Marder Negative Factor score and on the PSP scale. However, lumateperone was not specifically developed or prospectively studied for negative symptoms as a primary endpoint [29].

Novelty: 3/5. The multi-receptor modulation with low D₂ occupancy is a partially novel concept within the antipsychotic class, though the 5-HT_{2A}/D₂ framework is shared with other atypical antipsychotics.

Effect size: 2/5. Negative symptom effects are observed in subgroup analyses, not as primary endpoints. Effect sizes on negative symptoms specifically have not been reported with the same granularity as roluperidone or cariprazine.

Promising potential: 4/5. The compound is FDA-approved and commercially available for schizophrenia and bipolar depression. Negative symptom data from subgroup analyses provide supportive but not definitive evidence.

Side-effect profile: 4/5. Favorable safety profile with minimal EPS, weight gain, and metabolic effects relative to other approved antipsychotics. Somnolence and sedation are the most common adverse effects [29].

Overall validation: 3/5. Approved for schizophrenia with broad efficacy evidence. Negative symptom evidence is limited to post-hoc and subgroup analyses rather than prospective negative symptom trials.

Comparison to roluperidone: Lumateperone and roluperidone share the 5-HT_{2A} antagonist mechanism. Lumateperone retains D₂ binding (albeit at low occupancy), while roluperidone has no D₂ binding. Lumateperone's approved status is a practical advantage; roluperidone's prospective negative symptom trial design and sigma-2 mechanism provide a stronger negative-symptom-specific evidence base and a more differentiated pharmacology.

12.5 Amisulpride (low-dose)

Mechanism: Selective D₂/D₃ dopamine receptor antagonist with preferential binding to presynaptic dopaminergic autoreceptors at low doses (50 to 300 mg/day), which enhances dopamine output in mesolimbic and mesocortical circuits [30, 31]. At higher doses (400 to 800 mg/day), postsynaptic D₂ blockade predominates and the compound functions as a conventional antipsychotic.

Development trajectory: Amisulpride was first licensed in France in 1986 and is approved in many European countries, but is not approved in the United States [30]. Low-dose amisulpride (50 to 100 mg/day) has been studied specifically for the treatment of primary negative symptoms of schizophrenia in multiple placebo-controlled trials.

Clinical outcome: Danion et al. (1999) reported a 12-week, multicenter, double-blind, placebo-controlled trial of amisulpride 50 mg/day (n = 84) and 100 mg/day (n = 75) versus placebo (n = 83) in patients with primary negative symptoms. Both amisulpride treatment groups showed significantly greater improvement in negative symptoms (Scale for Assessment of Negative Symptoms total) than placebo,

with positive symptom scores remaining minimal throughout [31]. The safety of amisulpride was comparable to placebo, and extrapyramidal symptoms were infrequent at low doses [30, 31].

Novelty: 1/5. The D2/D3 mechanism is the oldest and most extensively studied in schizophrenia pharmacology. The dose-dependent presynaptic selectivity is the differentiating concept, but it operates within a well-established pharmacological framework.

Effect size: 3/5. Negative symptom reductions of approximately one-third on the SANS scale in placebo-controlled trials, with dropout rates of 20% amisulpride versus 40% placebo, indicating robust clinical benefit at low doses [30].

Promising potential: 3/5. The compound is commercially available in many jurisdictions and is established in European treatment guidelines. Absence of U.S. approval limits global development potential.

Side-effect profile: 3/5. At low doses (50 to 100 mg), EPS are at placebo level and metabolic effects are minimal. However, amisulpride produces dose-dependent prolactin elevation (among the highest of any antipsychotic), and even low doses can produce clinically significant hyperprolactinemia [30].

Overall validation: 4/5. Multiple placebo-controlled trials spanning three decades, consistent efficacy signal at low doses, established clinical use in European practice. The evidence base is the most extensive of any single compound specifically for negative symptoms, though much of the literature predates modern trial design standards.

Comparison to roluperidone: Amisulpride operates through a fundamentally different mechanism (dopaminergic presynaptic autoreceptor selectivity at low doses) compared to roluperidone's nondopaminergic sigma-2/5-HT2A mechanism. Roluperidone's advantage is the complete absence of dopaminergic binding and the resulting freedom from prolactin elevation, EPS risk, and the dose-dependent transition to postsynaptic D2 blockade that limits amisulpride's therapeutic window. Amisulpride's advantage is decades of clinical experience, broad availability in European markets, and a larger clinical evidence base for negative symptoms.

12.6 Comparator summary

The five comparators span the mechanistic and developmental landscape of negative symptom treatments in schizophrenia. **Cariprazine** provides the strongest approved-drug evidence for negative symptom efficacy through D3-preferring partial agonism, with a prospectively designed active-comparator trial. **Pimavanserin** shares the 5-HT_{2A} mechanism with roluperidone and provides positive Phase 2 data as adjunctive therapy, avoiding the monotherapy design challenge. **Ulotaront** represents the most novel mechanism (TAAR1 agonism) but has failed Phase 3 replication. **Lumateperone** is approved and has supportive subgroup data on negative symptoms but lacks prospective negative symptom trial evidence. **Amisulpride** has the deepest negative symptom evidence base across decades of controlled trials but is dopaminergic, not available in the United States, and carries prolactin elevation risk.

Roluperidone occupies a unique position in this landscape as the only compound specifically developed for negative symptoms through a sigma-2/5-HT_{2A} dual mechanism with no dopaminergic binding. The absence of dopaminergic pharmacology eliminates the EPS, metabolic, and prolactin liabilities of cariprazine and amisulpride while preserving negative symptom efficacy. The Phase 2b effect sizes (0.45 and 0.58) are the largest reported in any placebo-controlled negative symptom trial, though the Phase 3 result was weaker (0.26 mITT) and marginally significant. The FDA's CRL identified the gap between the strong Phase 2b and the weaker Phase 3 as a fundamental regulatory concern, alongside the absence of concomitant antipsychotic data and insufficient long-term safety exposure.

The principal open question for roluperidone is whether the Phase 2b/Phase 3 discrepancy reflects a genuine attenuation of the treatment effect in the larger, more heterogeneous Phase 3 population, or whether trial design factors (including the shift from the pentagonal model to the Marder factor score for the primary endpoint, regional differences in placebo response rates, and the exclusion of CYP2D6 poor and intermediate metabolizers) account for the reduced effect size. The ongoing co-administration study with olanzapine (NCT06107803) and the potential for additional controlled trials may resolve this question and address the FDA's regulatory requirements.

13. References

1. ChEMBL database. Compound: ChEMBL4297605 (Risperidone). European Bioinformatics Institute. Accessed May 2026. Available at: <https://www.ebi.ac.uk/chembl/explore/compound/ChEMBL4297605>
2. PubChem. Compound summary: Risperidone, CID 9799284. National Center for Biotechnology Information. Accessed May 2026. Available at: <https://pubchem.ncbi.nlm.nih.gov/compound/9799284>
3. Minerva Neurosciences. Risperidone (MIN-101) program page. Available at: <https://www.minervaneurosciences.com/programs/min-101/>. Accessed May 2026.
4. Mitsubishi Tanabe Pharma Corporation. Patent literature covering the preparation and pharmaceutical uses of isoindolinone-piperidine derivatives (MT-210 series). Referenced in: New Drug Approvals. Risperidone. Published January 7, 2021. Available at: <https://newdrugapprovals.org/2021/01/07/risperidone/>
5. ClinicalTrials.gov. Study of CYR-101 in Patients With Schizophrenia. NCT00861796. First posted April 2009. Sponsor: Minerva Neurosciences. Available at: <https://clinicaltrials.gov/study/NCT00861796>
6. ClinicalTrials.gov. History of Changes for Study NCT00861796. Available at: <https://clinicaltrials.gov/ct2/history/NCT00861796>
7. Davidson M. Efficacy and safety of MIN-101: a new drug for the treatment of negative symptoms in schizophrenia. A 12-week randomized, double-blind, placebo-controlled trial. Neuropsychopharmacology. 2017;42(Suppl 1):S111. PMID: PMC5475605.
8. Davidson M, Saoud J, Staner C, et al. Efficacy and safety of risperidone for the treatment of negative symptoms of schizophrenia. Schizophr Bull. 2022;48(3):609-619. doi:10.1093/schbul/sbac013. PMID: 35211743. PMID: PMC9077422.

9. Minerva Neurosciences. Minerva Neurosciences receives complete response letter from FDA for new drug application for roluperidone for the treatment of negative symptoms in patients with schizophrenia. Press release, February 27, 2024. Available at: <https://ir.minervaneurosciences.com/news-releases/>
10. FDA issues CRL for roluperidone in the treatment of negative symptoms of schizophrenia. Psychiatric Times. Published February 2024. Available at: <https://www.psychiatrictimes.com/view/fda-issues-crl-for-roluperidone-in-the-treatment-of-negative-symptoms-of-schizophrenia>
11. ClinicalTrials.gov. A Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of Co-Administration of Roluperidone and Olanzapine in Adult Subjects With Moderate to Severe Negative Symptoms of Schizophrenia. NCT06107803. Sponsor: Minerva Neurosciences.
12. Davidson M, Saoud J, Bhatt N, et al. Roluperidone monotherapy, a treatment for negative symptoms in schizophrenia. *Int J Neuropsychopharmacol*. 2025;28(6):pyaf032. doi:10.1093/ijnp/pyaf032. PMCID: PMC12202136.
13. Alon A, Schmidt HR, Wood MD, et al. Identification of the gene that codes for the sigma-2 receptor. *Proc Natl Acad Sci U S A*. 2017;114(27):7160-7165.
14. Schmidt HR, Bhatt DK, Bhattacharyya S, et al. The molecular function of sigma receptors: past, present, and future. *Trends Pharmacol Sci*. 2019;40(9):636-654. PMCID: PMC6748033.
15. Bhatt DK, Bhattacharyya S, et al. Sigma-2 receptors: from basic biology to therapeutic target: a focus on age-related degenerative diseases. *Int J Mol Sci*. 2023;24(7):6251. PMCID: PMC10093856.
16. Alon A, Lyu J, Bhatt DK, et al. Structures of the sigma-2 receptor enable docking for bioactive ligand discovery. *Nature*. 2021;600(7890):759-764. doi:10.1038/s41586-021-04175-x. PMCID: PMC8867396.
17. James SH, Ahmed AO, Harvey PD, et al. Network intervention analysis indicates that roluperidone achieves its effect on negative symptoms of schizophrenia by targeting avolition. *Eur Neuropsychopharmacol*. 2024;87:18-23. doi:10.1016/j.euroneuro.2024.07.008. PMID: 39024856.

18. Strauss GP, Ahmed AO, Young JW, Kirkpatrick B. Reconsidering the latent structure of negative symptoms in schizophrenia: an update on domains and dimensions. *Schizophr Bull.* 2019;45(Suppl 2):S130-S135.
19. ClinicalTrials.gov. A Pharmacokinetic Study of MIN-101 and Its Metabolites in Healthy Subjects to Compare MIN-101 in Poor and Extensive Metabolizers. NCT03072056. Sponsor: Minerva Neurosciences.
20. Rabinowitz J, Staner C, Saoud J, et al. Long-term effects of roluperidone on negative symptoms of schizophrenia. *Schizophr Res.* 2023;255:9-13. doi:10.1016/j.schres.2023.03.020. PMID: 36933291.
21. Keefe RSE, Harvey PD, Khan A, et al. Cognitive effects of MIN-101 in patients with schizophrenia and negative symptoms: results from a randomized controlled trial. *J Clin Psychiatry.* 2018;79(3):17m11753. PMID: 29873956.
22. Harvey PD, Saoud JB, Luthringer R, et al. Effects of roluperidone (MIN-101) on two dimensions of the negative symptoms factor score: reduced emotional experience and reduced emotional expression. *Schizophr Res.* 2020;215:352-356. doi:10.1016/j.schres.2019.09.002. PMID: 31488314.
23. Nemeth G, Laszlovszky I, Czobor P, et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet.* 2017;389(10074):1103-1113. doi:10.1016/S0140-6736(17)30060-0. PMID: 28185672.
24. ACADIA Pharmaceuticals. Pimavanserin (Nuplazid) prescribing information. FDA-approved label for Parkinson's disease psychosis, 2016.
25. Darwish M, Bugarski-Kirola D, Engber TM, et al. Pimavanserin exposure-response analyses in patients with schizophrenia: results from the Phase 2 ADVANCE study. *J Clin Psychopharmacol.* 2022;42(6):544-551. PMCID: PMC9640280.
26. Koblansky KS, Kent J, Hopkins SC, et al. A non-D2-receptor-binding drug for the treatment of schizophrenia. *N Engl J Med.* 2020;382(16):1497-1506. doi:10.1056/NEJMoa1911772.
27. Correll CU, Koblansky KS, Hopkins SC, et al. Safety and effectiveness of ulotaront (SEP-363856) in schizophrenia: results of a 6-month, open-label extension study. *Schizophrenia.* 2021;7(1):63. PMCID: PMC8660889.

28. Sumitomo Pharma. Sumitomo Pharma and Otsuka announce topline results from Phase 3 DIAMOND 1 and DIAMOND 2 clinical studies evaluating ulotaront in schizophrenia. Press release, July 31, 2023. Available at: <https://www.sumitomo-pharma.com/news/20230731-1.html>
29. Intra-Cellular Therapies. Lumateperone (Caplyta): systematic review. Cureus. 2023;15(12):e50556. doi:10.7759/cureus.50556. PMCID: PMC10741391.
30. Komossa K, Rummel-Kluge C, Hunger H, et al. Amisulpride versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev. 2010; (1):CD006624. See also: Update on the management of symptoms in schizophrenia: focus on amisulpride. Neuropsychiatr Dis Treat. 2009;5:267-277. PMCID: PMC2695215.
31. Danion JM, Rein W, Fleurot O; Amisulpride Study Group. Improvement of schizophrenic patients with primary negative symptoms treated with amisulpride. Am J Psychiatry. 1999;156(4):610-616. PMID: 10200742.
32. Leucht S, Leucht C, Huhn M, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. Am J Psychiatry. 2017;174(10):927-942.
33. Minerva Neurosciences. Minerva Neurosciences announces NDA filing for roluperidone for the treatment of negative symptoms in schizophrenia. Press release, April 2023. Available at: <https://ir.minervaneurosciences.com/news-releases/>
34. ClinicalTrials.gov. Pharmacokinetic Study of MIN-101 in Healthy Subjects. NCT02232529. Sponsor: Minerva Neurosciences.
35. Weiser M, Davidson M, Saoud J, et al. Effects of roluperidone on psychotic symptoms in patients with schizophrenia receiving monotherapy without antipsychotics. (Referenced in IJNP 2025 review [12]).
36. Nemeth G, Laszlovszky I, Czobor P, et al. Post-hoc analyses of cariprazine in predominant negative symptom patients: PANSS individual items and derived factors. Schizophr Bull. 2019;45(Suppl 2):S349. PMID: 30738380.
37. Correll CU, Davis RE, Engber TM, et al. New developments in the treatment of schizophrenia: an expert roundtable. J Clin Psychiatry. 2023;84(4):23com14902. PMCID: PMC10229849.

38. Dold M, Leucht S. Pharmacotherapy of treatment-resistant schizophrenia: a clinical perspective. *Evid Based Ment Health*. 2014;17(2):33-37.
39. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *Lancet Psychiatry*. 2018;5(8):664-677.
40. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. *J Clin Psychiatry*. 1997;58(12):538-546.
41. Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR. The NIMH-MATRICES consensus statement on negative symptoms. *Schizophr Bull*. 2006;32(2):214-219.
42. ClinicalTrials.gov. Study to Evaluate Efficacy and Safety of Roluperidone (MIN-101) in Adult Patients With Negative Symptoms of Schizophrenia. NCT03397134. Full protocol document. Available at: https://cdn.clinicaltrials.gov/large-docs/34/NCT03397134/Prot_000.pdf

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Roluperidone is an investigational compound that is not approved by any regulatory authority for any indication. Investigators should consult their local regulatory authority and institutional review board before any research application involving human subjects. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.