

RESEARCH MONOGRAPH . COMPOUND PROFILE

Ulotaront

A first-in-class TAAR1/5-HT1A dual agonist discovered through phenotypic screening, developed for schizophrenia under FDA Breakthrough Therapy Designation, and distinguished from all approved antipsychotics by the absence of dopamine D2 and serotonin 5-HT2A receptor antagonism.

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ABSTRACT

Ulotaront (SEP-363856) is a thienopyran-based small molecule and the first trace amine-associated receptor 1 (TAAR1) agonist to reach Phase 3 clinical development for the treatment of schizophrenia. Discovered through a target-agnostic phenotypic screening collaboration between PsychoGenics and Sunovion Pharmaceuticals (now Sumitomo Pharma), ulotaront was identified using the SmartCube automated behavioral platform rather than rational design against TAAR1, and its molecular target was subsequently deconvoluted to reveal full agonism at human TAAR1 (EC₅₀ approximately 38 to 140 nM, E_{max} approximately 101 to 109 percent) and partial agonism at the serotonin 5-HT_{1A} receptor (EC₅₀ approximately 2.3 micromolar, E_{max} approximately 75 percent). The compound is not an antagonist at either the dopamine D₂ or the serotonin 5-HT_{2A} receptor, the two canonical targets of all currently approved first-generation and second-generation antipsychotics. This mechanistic distinction positions ulotaront as a fundamentally novel pharmacological approach to psychotic disorders, with a preclinical and early clinical profile that suggests potential advantages in the avoidance of extrapyramidal symptoms, metabolic syndrome, hyperprolactinemia, and sedation that limit the tolerability of existing antipsychotic therapies.

In preclinical models, ulotaront dose-dependently reduced phencyclidine-induced hyperlocomotion, restored prepulse inhibition deficits, increased social interaction in chronic phencyclidine paradigms, and ameliorated cognitive impairments, all without producing catalepsy at doses up to 100 mg/kg. The

compound prevented olanzapine-induced weight gain in rodents and demonstrated no effect on prolactin release.

Pharmacokinetics are characterized by rapid oral absorption, greater than 70 percent bioavailability in preclinical species, high blood-brain barrier penetration (brain concentrations approximately threefold higher than plasma), a median effective half-life of approximately 7 hours in humans supporting once-daily dosing, and predominant hepatic metabolism through CYP2D6. The compound received FDA Breakthrough Therapy Designation in May 2019 on the basis of a positive Phase 2 randomized controlled trial (Koblan et al., 2020) in 245 acutely psychotic adults with schizophrenia, in which ulotaront at 50 to 75 mg/day produced a statistically significant reduction in Positive and Negative Syndrome Scale (PANSS) total score of 17.2 points versus 9.7 points on placebo at four weeks (effect size 0.45, p less than 0.001), with concurrent improvement on negative symptom, depressive symptom, and global severity measures. A 26-week open-label extension demonstrated sustained improvement (PANSS total reduction of 41.8 points from double-blind baseline) with a favorable metabolic and movement disorder safety profile.

The Phase 3 DIAMOND program, however, produced negative results. DIAMOND 1 (ulotaront 50 and 75 mg/day versus placebo in 435 patients) and DIAMOND 2 (ulotaront 75 and 100 mg/day versus placebo in 464 patients) both failed to meet their primary endpoints at six weeks, with large placebo responses potentially masking the therapeutic signal. Additional Phase 3 studies (DIAMOND 3, long-term extension, and a switch study versus quetiapine) were planned or ongoing at the time of the negative readouts. Despite the Phase 3 setback in schizophrenia, ulotaront continues in Phase 2/3 development for generalized anxiety disorder and as adjunctive therapy in major depressive disorder,

reflecting the broader neuropsychiatric potential of the TAAR1 mechanism. This monograph reviews the chemistry, discovery, molecular pharmacology, comprehensive pharmacokinetics, preclinical and clinical evidence across all studied indications, sourcing and handling considerations, stack interactions, adverse events, and a comparative assessment of five alternative approaches to non-dopaminergic antipsychotic pharmacology against ulotaront on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Ulotaront.

Development codes: SEP-363856, SEP-856. The development code SEP-363856 is the canonical identifier in the clinical literature and on ClinicalTrials.gov registrations. The abbreviated form SEP-856 appears in some early pharmacology publications [1, 2].

Chemical Abstracts Service registry numbers: 1310426-33-5 (free base), 1310422-41-3 (hydrochloride salt). The free base is the pharmacologically characterized form; the hydrochloride is the formulated salt used in clinical and research preparations.

International Union of Pure and Applied Chemistry name: (7S)-N-methyl-1-(4,5,6,7-tetrahydrothieno[3,2-c]pyran-7-yl)methanamine. Alternative systematic names include 1-[(7S)-5,7-dihydro-4H-thieno[2,3-c]pyran-7-yl]-N-methylmethanamine, reflecting different ring-numbering conventions for the thienopyran core.

PubChem CID: 89532783.

1.2 Structural class and chemistry

Ulotaront is a thienopyran derivative, comprising a thiophene ring fused to a dihydropyran ring with an N-methylaminomethyl substituent at the 7-position. The compound is structurally simple relative to most antipsychotic agents and does not contain any of the pharmacophoric elements characteristic of dopamine D2 receptor antagonists (no butyrophenone, no phenothiazine, no benzisoxazole, no dibenzodiazepine scaffold).

Molecular formula: C₉H₁₃NOS (free base); C₉H₁₄ClNOS (hydrochloride salt).

Molecular weight: 183.27 g/mol (free base); 219.73 g/mol (hydrochloride salt).

Physical properties: The free base is a small molecule with high aqueous solubility and high permeability, designated as a Biopharmaceutics Classification System (BCS) Class 1 compound by the United States Food and Drug Administration [3]. Lipophilicity (XLogP) is approximately 0.51, topological polar surface area is 49.5 square angstroms, hydrogen bond acceptors number 2, hydrogen bond donors number 1, and rotatable bonds number 2. The compound satisfies all Lipinski rule-of-five criteria with zero violations [4].

SMILES: CNCC1OCCc2c1scc2.

Stereochemistry: Ulotaront contains one stereocenter at carbon 7 of the thienopyran ring and is supplied as the single (S)-enantiomer. The (S)-enantiomer demonstrates approximately 17-fold greater potency at TAAR1 than the (R)-enantiomer [1]. Investigators acquiring research-grade ulotaront should confirm enantiomeric purity by chiral high-performance liquid chromatography or polarimetry.

1.3 Synthesis

The synthesis of ulotaront has not been published in full detail in the open literature. The compound was identified from a library of thienopyran derivatives evaluated in the SmartCube phenotypic screening platform at PsychoGenics [1, 5]. The thienopyran core is accessible through established heterocyclic synthesis strategies involving cyclization of appropriately substituted thiophene precursors with aldehydes or epoxides to form the pyran ring, followed by introduction of the aminomethyl substituent through reductive amination or nucleophilic displacement. The N-methyl group is introduced by standard methylation of the primary amine or by use of methylamine in the reductive amination step. Resolution of the racemic mixture to obtain the (S)-enantiomer is accomplished by chiral chromatography or by asymmetric synthesis using chiral auxiliaries or catalysts. The N-demethylated analogue (SEP-383103) has been identified as the primary metabolite and shows enhanced TAAR1 potency (EC₅₀ approximately 3.5 nM) relative to the parent compound [1].

2. Abstract

Ulotaront (SEP-363856) is a first-in-class dual agonist of the trace amine-associated receptor 1 (TAAR1) and the serotonin 5-HT_{1A} receptor, discovered through phenotypic screening by PsychoGenics and developed by Sunovion Pharmaceuticals (subsequently Sumitomo Pharma) in collaboration with Otsuka Pharmaceutical for the treatment of schizophrenia and other neuropsychiatric disorders [1, 5, 6]. The compound is mechanistically unique among antipsychotic candidates in that it does not antagonize dopamine D₂ or serotonin 5-HT_{2A} receptors, the molecular targets shared by all currently approved first-generation and second-generation antipsychotic medications.

The molecular pharmacology of ulotaront centers on full agonism at human TAAR1 (EC₅₀ 38 to 140 nM, E_{max} 101 to 109 percent) and partial agonism at 5-HT_{1A} (EC₅₀ approximately 2.3 micromolar, E_{max} approximately 75 percent), with weak partial agonist activity at dopamine D₂ receptors at concentrations approximately 100-fold higher than the TAAR1 EC₅₀ [1, 2, 7]. TAAR1 is a G-protein-coupled receptor expressed in cortical, limbic, and midbrain monoaminergic regions; its activation produces negative modulation of dopaminergic, serotonergic, and glutamatergic neurotransmission through presynaptic inhibition of neuronal firing and neurotransmitter release, providing an indirect and physiologically constrained regulation of dopaminergic circuits rather than the direct postsynaptic dopamine receptor blockade characteristic of conventional antipsychotics [8, 9].

In preclinical models, ulotaront demonstrated antipsychotic-like efficacy (phencyclidine-induced hyperlocomotion reversal, prepulse inhibition restoration, social interaction normalization) without catalepsy induction at doses up to 100 mg/kg, supporting the absence of extrapyramidal liability [1, 10]. Chronic treatment did not produce weight gain and prevented olanzapine-induced weight gain in rodent models [10].

The pivotal Phase 2 trial (Koblan et al., 2020; SEP361-201) in 245 acutely psychotic adults with schizophrenia demonstrated statistically significant improvement on the PANSS total score at four weeks (mean change: ulotaront minus 17.2 points versus placebo minus 9.7 points; effect size 0.45; *p* less than 0.001), with concurrent benefit on positive, negative, depressive, and global severity measures [6]. A 26-

week open-label extension confirmed sustained improvement (PANSS total reduction of 41.8 points) with a safety profile notable for the absence of clinically significant weight gain, prolactin elevation, metabolic derangement, or movement disorders [11].

The Phase 3 DIAMOND program in acute schizophrenia, however, produced two negative trials. DIAMOND 1 (435 patients, 6 weeks, ulotaront 50 and 75 mg/day versus placebo) and DIAMOND 2 (464 patients, 6 weeks, ulotaront 75 and 100 mg/day versus placebo) both failed to demonstrate statistically significant separation from placebo on the PANSS total score primary endpoint, potentially attributable to large placebo responses [12]. Despite these negative Phase 3 readouts, the compound continues in Phase 2/3 development for generalized anxiety disorder and adjunctive major depressive disorder, reflecting the broader potential of the TAAR1 mechanism across neuropsychiatric conditions [13].

3. Discovery and Development History

3.1 Origin and phenotypic discovery

Ulotaront was discovered through a collaboration between PsychoGenics, Inc. (Paramus, New Jersey) and Sunovion Pharmaceuticals (Marlborough, Massachusetts) using a target-agnostic, phenotypic screening approach [5]. The SmartCube platform, a proprietary high-throughput behavioral assay system developed by PsychoGenics, evaluates compounds for antipsychotic-like behavioral signatures in mice through automated tracking and machine-learning classification of behavioral responses across multiple domains. Ulotaront was identified from a chemical library as producing a behavioral signature consistent with antipsychotic activity but pharmacologically distinct from D2 receptor antagonists. The molecular target was subsequently deconvoluted to TAAR1 and 5-HT1A through receptor panel screening, radioligand displacement assays, and functional pharmacology in heterologous expression systems [1].

The target-agnostic discovery origin is notable. Ulotaront was not designed as a TAAR1 agonist; rather, the phenotypic screening platform identified the compound on the basis of its behavioral profile, and the TAAR1 mechanism was established retrospectively. This discovery pathway contrasts with the rational-design approach that produced other TAAR1 agonists such as ralmitaront (RO6889450), which was designed by Roche as a selective TAAR1 partial agonist [14].

3.2 Preclinical development

Sunovion advanced ulotaront through standard preclinical pharmacology and toxicology. The compound demonstrated efficacy in multiple rodent models relevant to schizophrenia: reduction of phencyclidine-induced hyperlocomotion (0.3 to 3 mg/kg), restoration of prepulse inhibition (minimum effective dose 3 mg/kg), reversal of social interaction deficits in chronic phencyclidine models, and amelioration of cognitive impairments at 10 mg/kg [1, 10]. The absence of catalepsy at doses up to 100 mg/kg (the highest dose tested) confirmed the lack of D2-mediated extrapyra-

midal liability. Chronic administration did not produce weight gain, hyperprolactinemia, or metabolic derangement, and the compound prevented olanzapine-induced weight gain in co-administered rodent models [10].

3.3 Clinical development

Phase 1 studies in healthy volunteers established safety, tolerability, and pharmacokinetics supporting once-daily oral dosing. A Phase 1 REM sleep study demonstrated robust suppression of rapid eye movement sleep parameters at 50 mg with large effect sizes (greater than 3), consistent with TAAR1-mediated monoaminergic modulation and guiding dose selection for subsequent efficacy trials [15].

The Phase 2 randomized, double-blind, placebo-controlled trial (SEP361-201; Koblan et al., 2020) enrolled 245 acutely psychotic inpatients with schizophrenia (ages 18 to 40) and demonstrated statistically significant efficacy at four weeks, leading to FDA Breakthrough Therapy Designation in May 2019 [6]. The 26-week open-label extension (SEP361-202) enrolled 157 patients and demonstrated continued efficacy and favorable tolerability [11].

3.4 Phase 3 program and negative readouts

The Phase 3 DIAMOND program comprised multiple studies: DIAMOND 1 (SEP361-301; 525 patients randomized, fixed doses 50 and 75 mg/day, 6-week inpatient study), DIAMOND 2 (SEP361-302; 462 patients randomized, fixed doses 75 and 100 mg/day, 6-week inpatient study), a 52-week extension (SEP361-303), a long-term safety study (SEP361-304), and a switch study comparing ulotaront to quetiapine XR [12, 16]. In July 2023, Sumitomo Pharma and Otsuka announced that both DIAMOND 1 and DIAMOND 2 had failed to meet their primary endpoint of statistically significant reduction in PANSS total score versus placebo. Numerically larger reductions were observed with ulotaront in DIAMOND 2 (LS mean: minus 16.4 and minus 18.1 at 75 and 100 mg/day, respectively, versus minus 14.3 for placebo), but the differences did not reach statistical significance. A large placebo response was noted as a potential contributor to the negative outcome [12].

3.5 Ongoing development

Despite the Phase 3 failures in acute schizophrenia, Sumitomo Pharma has continued development of ulotaront in other neuropsychiatric indications. Phase 2/3 trials are evaluating ulotaront for generalized anxiety disorder (434 participants, 50 to 75 mg/day, 8-week primary endpoint on the Hamilton Anxiety Rating Scale) and as adjunctive therapy in major depressive disorder [13]. A proof-of-concept study in Parkinson's disease psychosis (38 patients) showed improvements across several measures without motor symptom worsening, though the study was not powered for statistical significance [17].

4. Mechanism of Action

Ulotaront is a multi-target ligand with principal activity at TAAR1 and 5-HT1A receptors. Its mechanism of action is fundamentally distinct from all approved antipsychotics and represents the first clinical validation of TAAR1 as a pharmacological target in psychotic disorders.

4.1 TAAR1 agonism

The trace amine-associated receptor 1 (TAAR1) is an intracellular G-protein-coupled receptor (Gs-coupled, activating adenylate cyclase) expressed in cortical, limbic, and midbrain monoaminergic nuclei, including the ventral tegmental area, substantia nigra, dorsal raphe nucleus, locus coeruleus, and prefrontal cortex [8, 9]. TAAR1 is activated by endogenous trace amines (phenylethylamine, tyramine, tryptamine, octopamine) and by monoamine neurotransmitters (dopamine, serotonin, norepinephrine) at supraphysiological concentrations. The receptor functions as a presynaptic rheostat that negatively modulates dopaminergic, serotonergic, and glutamatergic neurotransmission [8].

Ulotaront is a full agonist at human TAAR1. Reported EC₅₀ values range from 38 plus or minus 11 nM (NanoBiT G protein recruitment assay) to 140 plus or minus 62 nM (cAMP accumulation assay), with maximal efficacy (E_{max}) of 101 to 109 percent relative to the endogenous agonist phenylethylamine [1, 2, 7]. In G-protein-coupled inwardly rectifying potassium (GIRK) channel activation assays, ulotaront demonstrated a relative efficacy of 0.91 plus or minus 0.04 with a pEC₅₀ of 6.42 plus or minus 0.10 [7].

The downstream consequences of TAAR1 activation in midbrain dopaminergic neurons include reduction of neuronal firing rate and dopamine release in the striatum and nucleus accumbens, producing antipsychotic-like behavioral effects (hyperlocomotion suppression, prepulse inhibition normalization) without direct postsynaptic D2 receptor blockade [8, 9]. This presynaptic, modulatory mechanism preserves physiological dopaminergic transmission while constraining pathological hyperdopaminergic states, which is the theoretical basis for the anticipated absence of extrapyramidal symptoms, tardive dyskinesia, and hyperprolactinemia [9].

4.2 Serotonin 5-HT1A partial agonism

Ulotaront is a partial agonist at the serotonin 5-HT1A receptor, with an EC50 of approximately 2.3 plus or minus 1.4 micromolar and Emax of approximately 74.7 plus or minus 19.6 percent in cAMP assays [1, 2]. The 5-HT1A receptor is a Gi-coupled receptor expressed on serotonergic neurons of the raphe nuclei (somatodendritic autoreceptor) and on postsynaptic neurons in cortex, hippocampus, and limbic regions. Agonism at somatodendritic 5-HT1A autoreceptors reduces serotonergic firing and is the basis for the anxiolytic and antidepressant activity of buspirone and related azapirones; postsynaptic 5-HT1A activation in cortex and hippocampus has procognitive and mood-stabilizing properties [18].

The 5-HT1A agonist activity of ulotaront, though approximately 10-fold less potent than its TAAR1 activity, is pharmacologically relevant at clinical doses and may contribute to the negative symptom and depressive symptom improvement observed in clinical trials [6]. The combination of TAAR1 and 5-HT1A agonism is unique to ulotaront among clinical-stage compounds; ralmitaront, the other TAAR1 agonist that reached Phase 2, lacks detectable 5-HT1A activity [7].

4.3 Dopamine D2 receptor activity

Ulotaront exhibits weak partial agonist activity at the dopamine D2 receptor at concentrations approximately 100-fold higher than the TAAR1 EC50 (pEC50 4.92 plus or minus 0.08 in NanoBiT assay; 29 plus or minus 9 percent maximal cAMP inhibition) [7]. In primate brain imaging studies, ulotaront produced very low D2 receptor occupancy levels (less than 10 percent) at pharmacologically active doses, confirming that D2 receptor engagement is not a meaningful contributor to the clinical pharmacology [1, 10].

4.4 Additional receptor activities

Ulotaront demonstrates agonist activity at the serotonin 5-HT1D receptor (EC50 approximately 262 nM) [2]. No significant activity has been reported at serotonin 5-HT2A, 5-HT2C, histamine H1, muscarinic M1 to M5, or adrenergic alpha-1 or alpha-2 receptors at concentrations relevant to clinical dosing. The absence of 5-HT2A antagonism, H1 antagonism, and muscarinic antagonism distinguishes ulotaront

from second-generation antipsychotics and is the pharmacological basis for the anticipated absence of sedation, weight gain, and anticholinergic adverse effects [1, 10].

4.5 Composite pharmacology

The composite pharmacology at clinical doses (50 to 100 mg/day) produces estimated plasma concentrations that achieve near-complete TAAR1 occupancy, partial 5-HT_{1A} occupancy, and negligible D₂ occupancy. Brain concentrations exceed plasma concentrations by approximately threefold in preclinical species, further supporting central TAAR1 and 5-HT_{1A} engagement [3]. The net effect is indirect downregulation of hyperdopaminergic and hyperglutamatergic states through TAAR1-mediated presynaptic modulation, combined with anxiolytic and mood-stabilizing effects through 5-HT_{1A} agonism, without the direct receptor blockade that produces the cardinal adverse effects of conventional and atypical antipsychotics.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Ulotaront is well absorbed after oral administration. The compound has high aqueous solubility and high membrane permeability, consistent with its BCS Class 1 designation [3]. In preclinical species, oral bioavailability exceeds 70 percent with rapid absorption (Tmax approximately 15 minutes in rats at 10 mg/kg) [3]. In human population pharmacokinetic analysis, ulotaront demonstrates dose-proportional pharmacokinetics across the 25 to 100 mg dose range, with estimated median Tmax of 2.8 hours and dose proportionality supporting once-daily administration [15, 16].

5.2 Distribution

Volume of distribution in preclinical species is approximately 3.5 liters per kilogram, indicating substantial tissue partitioning [3]. Plasma protein binding is low; the unbound fraction exceeds 78 percent, a property that favors tissue distribution and central nervous system penetration [3]. The compound demonstrates good penetration across the blood-brain barrier in mice and rats. In rats receiving 10 mg/kg orally, brain concentrations and brain area under the curve (AUC) were approximately threefold higher than in plasma, with equivalent Tmax values (15 minutes) in both compartments. The brain-to-plasma concentration ratio exceeds unity, supporting the central pharmacological activity observed at clinical doses [3].

5.3 Metabolism

Ulotaront undergoes hepatic metabolism through both NADPH-dependent (cytochrome P450-mediated) and NADPH-independent pathways [3]. CYP2D6 is the major metabolizing enzyme, a finding with clinical implications for CYP2D6 polymorphism (discussed in Section 10). The primary metabolite is SEP-383103 (the N-demethylated analogue), which retains TAAR1 agonist activity with enhanced potency (EC50 approximately 3.5 nM, compared to 38 to 140 nM for ulotaront) [1]. The

pharmacological significance of the active metabolite in the overall clinical effect has not been fully characterized but may contribute to sustained TAAR1 engagement beyond the parent compound's plasma residence.

Ulotaront is an inducer of CYP2B6, an inhibitor of CYP2D6, and an inhibitor of organic cation transporters OCT1 and OCT2. The primary metabolite SEP-383103 is neither a CYP inducer nor a potent inhibitor of CYPs or human transporters [3].

5.4 Elimination

In preclinical species, the elimination half-life ranges from 1.5 to 4 hours with clearance of 12 to 43 mL/min/kg [3]. In human population pharmacokinetic analysis, the median effective half-life is approximately 7 hours, supporting once-daily dosing [15]. The elimination is predominantly hepatic (metabolic) rather than renal.

5.5 Routes of administration

Ulotaront has been administered exclusively by the oral route in clinical development. Capsule formulations at 25 mg, 50 mg, 75 mg, and 100 mg strengths have been used across Phase 1, Phase 2, and Phase 3 studies. No intravenous, intramuscular, or subcutaneous formulation has been developed.

5.6 Special populations

The Phase 2 trial enrolled patients aged 18 to 40 years; the Phase 3 DIAMOND program enrolled adults aged 18 to 65 years [6, 12]. Dedicated pediatric, geriatric, hepatic impairment, and renal impairment pharmacokinetic studies have not been published in the peer-reviewed literature as of the most recent monograph revision. Given the predominant CYP2D6 metabolism, CYP2D6 poor metabolizers (approximately 5 to 10 percent of European-ancestry populations) are expected to have substantially elevated plasma concentrations of the parent compound, with implications for dose adjustment (see Section 10).

6. Preclinical Pharmacology

6.1 Psychosis models

Ulotaront demonstrated broad efficacy in rodent models of psychosis-relevant behaviors. In the phencyclidine (PCP)-induced hyperlocomotion assay, ulotaront decreased hyperlocomotion in a dose-dependent manner at doses of 0.3 to 3 mg/kg [1, 10]. In the prepulse inhibition (PPI) paradigm, ulotaront dose-dependently increased PPI with a minimum effective dose of 3 mg/kg [10]. In the amphetamine-induced hyperlocomotion model, ulotaront similarly reduced pathological locomotor activation [1].

6.2 Negative symptom and cognitive models

In a chronic PCP model of social interaction deficit (a translational model for negative symptoms of schizophrenia), ulotaront increased social interaction time [10]. In cognitive paradigms, the compound ameliorated cognitive impairments caused by subchronic PCP treatment at 10 mg/kg [10]. These findings are consistent with the clinical observation of negative symptom improvement in the Phase 2 trial (BNSS total score effect size 0.48) and support the hypothesis that TAAR1 agonism addresses a broader symptom domain than D2 antagonism alone [6].

6.3 Catalepsy and extrapyramidal assessment

Critically, ulotaront produced no catalepsy in mice at the highest studied dose of 100 mg/kg, in contrast to haloperidol and other D2 antagonists that produce catalepsy at pharmacologically active doses [10]. This finding is the principal pre-clinical evidence supporting the absence of extrapyramidal symptom liability and is consistent with the very low D2 receptor occupancy (less than 10 percent) observed in primate brain imaging [1].

6.4 Metabolic and endocrine effects

Chronic treatment with ulotaront at 2 to 3 mg/kg was not associated with weight gain in rodent models [10]. In a co-administration paradigm, ulotaront prevented weight gain in animals chronically treated with olanzapine, suggesting a potential protective role against second-generation antipsychotic-induced metabolic syndrome [10]. No effects on prolactin release were observed, consistent with the absence of D2 receptor blockade.

6.5 Dopamine synthesis capacity

Ulotaront reduced striatal dopamine synthesis capacity as measured by [18F]-DOPA positron emission tomography in rodent models, consistent with TAAR1-mediated presynaptic modulation of dopaminergic neurotransmission [9]. This mechanism is distinct from the postsynaptic D2 blockade that characterizes conventional antipsychotics and supports the hypothesis that TAAR1 agonism constrains pathological dopaminergic hyperactivity through an upstream, modulatory mechanism.

6.6 Sleep architecture

Ulotaront produced marked suppression of rapid eye movement (REM) sleep in rodent and human studies, consistent with TAAR1-mediated effects on monoaminergic tone in brainstem sleep-regulating nuclei [15]. The REM-suppressing property was the basis for exploratory development in narcolepsy with cataplexy, although the narcolepsy clinical program was subsequently discontinued after a Phase 1b crossover study did not demonstrate meaningful improvement in sleepiness measures despite confirmed REM reduction [19].

6.7 Abuse liability

Ulotaront lacks abuse liability in standard preclinical assessments and attenuates cocaine cue-induced relapse in rats, supporting a favorable profile for chronic outpatient administration and suggesting a potential role in substance use disorder research [20].

7. Clinical Evidence Base

7.1 Phase 2 acute schizophrenia trial (Koblan et al., 2020)

The pivotal Phase 2 trial (SEP361-201; NCT02969382) was a 4-week, randomized, double-blind, placebo-controlled study in 245 acutely psychotic inpatients with schizophrenia, aged 18 to 40 years [6]. Patients were randomized to ulotaront (flexible dosing, 50 or 75 mg once daily) or placebo. Baseline mean PANSS total score was approximately 101 (positive subscale 26, negative subscale 25).

Primary endpoint: Change from baseline in PANSS total score at Week 4. Ulotaront produced a least-squares mean reduction of 17.2 points versus 9.7 points for placebo (difference: minus 7.5 points; 95 percent confidence interval minus 11.9 to minus 3.0; p less than 0.001; effect size 0.45) [6].

Secondary endpoints: Statistically significant improvements were observed across all secondary measures: PANSS positive subscale (effect size 0.32), PANSS negative subscale (effect size 0.37), Brief Negative Symptom Scale (BNSS) total (effect size 0.48), Clinical Global Impressions-Severity (CGI-S) (effect size 0.52), and Montgomery-Asberg Depression Rating Scale (MADRS) (effect size 0.32) [6, 16]. Separation from placebo was observed by Week 3 on the PANSS total score.

Post-hoc negative symptom analysis: A UPSM-transformed analysis demonstrated that the negative symptom improvement (on both apathy/avolition and deficit-of-expression subfactors) was independent of positive symptom change, supporting a direct effect of ulotaront on negative symptoms rather than a secondary consequence of positive symptom improvement [16].

7.2 Open-label extension (26 weeks)

The open-label extension study (SEP361-202) enrolled 157 patients from the Phase 2 trial (78 prior ulotaront, 79 switched from placebo) for 26 weeks of flexible-dose treatment at 25, 50, or 75 mg/day [11].

Efficacy: Continued improvement was observed over 26 weeks. At endpoint (observed cases), PANSS total score reduction from the original double-blind baseline was 41.8 points. BNSS total reduction was 16.8 points. CGI-S improvement was 2.0

points. Responder rates (30 percent or greater PANSS total score reduction from baseline) were 93.3 percent, and stringent responder rates (50 percent or greater PANSS total score reduction) were 72.1 percent [11]. The Kaplan-Meier estimate of the probability of relapse among responders at 26 weeks was 0.23 (95 percent confidence interval 0.13 to 0.38) [11].

Safety (26 weeks): Mean weight change was minus 0.3 kg (standard deviation 3.7). Mean BMI change was minus 0.1 kg/m². Prolactin decreased (females minus 3.4 ng/mL, males minus 2.7 ng/mL). Total cholesterol decreased by 2.0 mg/dL, LDL cholesterol by 9.0 mg/dL, triglycerides by 5.0 mg/dL, and HbA1c showed no change (0.0 percent). Movement disorder rating scales showed minimal changes: Simpson-Angus Scale minus 0.0, Barnes Akathisia Rating Scale minus 0.1, Abnormal Involuntary Movement Scale 0.0 [11].

7.3 Phase 3 DIAMOND program (acute schizophrenia)

DIAMOND 1 (SEP361-301): A 6-week, randomized, double-blind, placebo-controlled study of ulotaront at fixed doses of 50 mg/day and 75 mg/day versus placebo in 435 acutely psychotic adults with schizophrenia [12]. The study did not meet its primary endpoint of statistically significant reduction in PANSS total score versus placebo at Week 6.

DIAMOND 2 (SEP361-302): A 6-week, randomized, double-blind, placebo-controlled study of ulotaront at fixed doses of 75 mg/day and 100 mg/day versus placebo in 464 acutely psychotic adults with schizophrenia [12]. The study did not meet its primary endpoint. Numerical reductions in PANSS total score were larger with ulotaront (LS mean: minus 16.4 at 75 mg/day, minus 18.1 at 100 mg/day) than with placebo (minus 14.3), but the differences were not statistically significant. A large placebo response was noted across both studies.

The negative Phase 3 results contrast with the positive Phase 2 outcome. Potential explanations include the larger sample sizes and broader inclusion criteria in Phase 3, the fixed (versus flexible) dosing design, the 6-week (versus 4-week) treatment duration, and the higher placebo response rates observed in multi-center global schizophrenia trials conducted in the post-COVID period [12].

7.4 Parkinson's disease psychosis

A proof-of-concept study in 38 patients with Parkinson's disease psychosis demonstrated improvements across several efficacy measures without worsening of motor symptoms, though the study was not statistically powered for definitive efficacy conclusions [17]. The absence of motor symptom worsening is consistent with the non-D2-antagonist mechanism and represents a potential advantage over pimavanserin (the only FDA-approved therapy for Parkinson's disease psychosis, which itself does not block D2 but acts through 5-HT_{2A} inverse agonism).

7.5 Generalized anxiety disorder and major depressive disorder

Phase 2/3 trials are evaluating ulotaront for generalized anxiety disorder (434 participants, ulotaront 50 to 75 mg/day versus placebo for 8 weeks, primary endpoint HAM-A total score) and as adjunctive therapy in major depressive disorder [13]. These trials are ongoing; results have not been reported as of the most recent monograph revision.

7.6 Narcolepsy

A Phase 1b crossover trial evaluated ulotaront in narcolepsy with cataplexy on the basis of its REM sleep-suppressing properties [19]. Despite confirmed REM sleep suppression, the study did not demonstrate meaningful improvement in clinical sleepiness measures, and the narcolepsy program was discontinued.

7.7 QT interval assessment

A thorough QT study (NCT04369391) evaluated ulotaront at 150 mg (supratherapeutic dose) and demonstrated no clinically relevant effect on heart rate or electrocardiogram intervals, confirming cardiac safety at doses well above the therapeutic range [16].

8. Sourcing and Quality Verification

Ulotaront is not approved by any regulatory authority as of the most recent monograph revision. The compound is therefore not available as a pharmaceutical-grade medicine in any jurisdiction. All sourcing for research applications is through chemical research suppliers.

Research-grade ulotaront (free base and hydrochloride salt) is supplied by multiple chemical and pharmaceutical research suppliers (MedChemExpress, Cayman Chemical, Selleckchem, BOC Sciences, AbMole BioScience, MedKoo Biosciences, others) at greater than 98 percent purity by HPLC. Supply is typically in milligram to gram quantities. Pricing varies by supplier and quantity.

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

- High-performance liquid chromatography area-percent purity, targeting greater than 98 percent
- Mass spectrometry confirmation of molecular weight (184.27 for the protonated free base $[M+H]^+$, or 183.27 for the free base)
- Chiral HPLC or polarimetry confirmation of enantiomeric purity (greater than 99 percent enantiomeric excess of the (S)-enantiomer)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. Given the relatively simple structure and small molecular weight, counterfeit material is unlikely but enantiomeric impurity (contamination with the less active (R)-enantiomer) is a realistic concern that warrants routine verification.

9. Reconstitution and Handling

Ulotaront hydrochloride is expected to be soluble in water and dimethyl sulfoxide (DMSO) given its high aqueous solubility and BCS Class 1 designation. For in vitro research applications, stock solutions are typically prepared at 10 to 50 mM in DMSO or in aqueous buffer at appropriate pH. For in vivo rodent studies, the compound has been administered orally in standard vehicle formulations (methylcellulose suspensions, aqueous solutions) at doses ranging from 0.3 to 100 mg/kg.

Storage of the solid material should be at minus 20 degrees Celsius or 2 to 8 degrees Celsius, protected from moisture. DMSO stock solutions should be aliquoted for single use to avoid freeze-thaw degradation, though the simple molecular structure suggests reasonable freeze-thaw stability. Aqueous solutions should be prepared fresh or used within standard stability windows (typically 24 to 48 hours at room temperature, up to 14 days refrigerated).

Light sensitivity has not been specifically characterized in published literature; light protection during storage is reasonable practice for research-grade material. The compound should be handled with standard laboratory precautions for pharmacologically active research chemicals.

10. Stack Interactions and Combinations

Ulotaront interacts with several drug classes through its CYP2D6-mediated metabolism and through its receptor pharmacology. Investigators should consider the following interactions:

CYP2D6 inhibitors and poor metabolizer phenotype: CYP2D6 is the major metabolizing enzyme for ulotaront [3]. Strong CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion, quinidine, terbinafine) are expected to substantially increase ulotaront exposure, analogous to the well-characterized CYP2D6 polymorphic phenotype observed with other CYP2D6 substrates. CYP2D6 poor metabolizers (approximately 5 to 10 percent of European-ancestry populations) are expected to have elevated plasma concentrations of the parent compound. Dose adjustment should be considered in known poor metabolizers and in the context of concurrent strong CYP2D6 inhibitor therapy.

CYP2D6 substrates: Ulotaront is an inhibitor of CYP2D6 [3]. Concurrent administration with other CYP2D6 substrates (codeine, tramadol, tamoxifen, dextromethorphan, metoprolol, atomoxetine) may alter the metabolism of the co-administered substrate.

CYP2B6 substrates: Ulotaront is an inducer of CYP2B6 [3]. Concurrent administration with CYP2B6 substrates (bupropion, efavirenz, cyclophosphamide) may reduce the exposure of the co-administered substrate.

OCT1 and OCT2 substrates: Ulotaront is an inhibitor of organic cation transporters OCT1 and OCT2 [3]. Concurrent administration with OCT substrates (metformin is the principal clinical OCT2 substrate) may increase the exposure of the co-administered substrate.

Serotonergic agents: The 5-HT_{1A} agonist activity introduces a theoretical risk of serotonergic interaction with concurrent serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, and other

serotonergic agents. Although the 5-HT_{1A} activity is partial and of moderate potency, the combination should be approached with awareness of the additive serotonergic potential.

Dopaminergic agents: Concurrent administration with D₂ antagonists (conventional and atypical antipsychotics) is of interest in switch-study designs and in augmentation strategies. The mechanistic complementarity (presynaptic TAAR1-mediated dopaminergic modulation plus postsynaptic D₂ blockade) has not been characterized in published combination-pharmacology studies. Concurrent dopamine agonists (pramipexole, ropinirole, rotigotine) for Parkinson's disease would be expected to partially oppose the indirect dopaminergic reduction produced by TAAR1 agonism.

QT-prolonging agents: The thorough QT study demonstrated no clinically relevant QT prolongation at supratherapeutic doses [16]. Concurrent use with QT-prolonging agents is therefore not anticipated to carry additive cardiac risk, but standard electrocardiographic monitoring is appropriate in investigational settings.

11. Adverse Events and Safety

11.1 Common adverse events (Phase 2, 4 weeks)

The overall adverse event rate in the Phase 2 trial was 45.8 percent with ulotaront versus 50.4 percent with placebo, indicating that the compound was not associated with a higher overall adverse event burden than placebo [6, 16]. Individual adverse events occurring at 2 percent or greater in the ulotaront group were:

- Somnolence: 6.7 percent (NNH 53)
- Agitation: 5.0 percent (NNH greater than 100)
- Nausea: 5.0 percent (NNH 56)
- Extrapyramidal symptoms: 3.3 percent (NNH greater than 100, not statistically different from placebo)
- Diarrhea: 2.5 percent (NNH 59)
- Dyspepsia: 2.5 percent (NNH 40)

Severe adverse events occurred in 5.8 percent of the ulotaront group versus 1.6 percent of the placebo group. Adverse-event-related discontinuation was 8.3 percent versus 6.4 percent. Serious adverse events were reported in 2 patients on ulotaront versus 4 on placebo [16].

11.2 Common adverse events (open-label extension, 26 weeks)

The most common adverse events occurring at 5 percent or greater during the 26-week extension were: schizophrenia worsening (12.2 percent), headache (11.5 percent), insomnia (8.3 percent), and anxiety (5.1 percent) [11]. Severe adverse events occurred in 5.1 percent of patients.

11.3 Metabolic and endocrine safety

The safety profile of ulotaront is distinguished from conventional and atypical antipsychotics by the absence of clinically significant metabolic effects. Over 26 weeks: mean weight change was minus 0.3 kg; BMI decreased by 0.1 kg/m²; total

cholesterol, LDL cholesterol, and triglycerides decreased modestly; HbA1c did not change; and prolactin levels decreased in both sexes [11]. This profile is in marked contrast to the weight gain, dyslipidemia, insulin resistance, and hyperprolactinemia that characterize second-generation antipsychotics (olanzapine, quetiapine, risperidone, clozapine) and that are the principal drivers of cardiovascular morbidity and treatment discontinuation in schizophrenia.

11.4 Movement disorder safety

Movement disorder rating scales showed no clinically meaningful changes over 26 weeks: Simpson-Angus Scale minus 0.0, Barnes Akathisia Rating Scale minus 0.1, Abnormal Involuntary Movement Scale 0.0 [11]. No difference between ulotaront and placebo was observed for the incidence of extrapyramidal symptoms in the Phase 2 trial [6, 16]. This profile is consistent with the preclinical absence of catalepsy and the very low D2 receptor occupancy.

11.5 Cardiac safety

The thorough QT study at a supratherapeutic dose of 150 mg demonstrated no clinically relevant effect on heart rate or electrocardiographic intervals [16]. No cardiac serious adverse events attributable to ulotaront have been reported in published clinical data.

11.6 Pregnancy and lactation

No human pregnancy or lactation data are available. The compound is in investigational status and has not received regulatory approval. Standard precautions for investigational compounds apply.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative approaches to non-dopaminergic or mechanistically novel antipsychotic pharmacology against ulotaront, evaluated on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation. The comparators were selected as the principal compounds with substantive clinical evidence or registration in schizophrenia that share ulotaront's goal of addressing unmet needs in tolerability, negative symptoms, or cognitive symptoms.

12.1 Ralmitaront (RO6889450)

Mechanism: TAAR1 partial agonist. Unlike ulotaront, ralmitaront lacks detectable 5-HT1A agonist activity and has no appreciable dopamine D2 activity [7, 14]. Developed by Roche through rational design as a selective TAAR1 ligand.

Development trajectory: Two Phase 2 trials were conducted in schizophrenia: one evaluating monotherapy for acute positive symptoms and one evaluating adjunctive treatment for negative symptoms. Both were terminated early after preliminary analyses indicated the primary endpoints were negative [14]. The compound is no longer in active clinical development.

Novelty: Moderate. TAAR1 partial agonism is mechanistically related to ulotaront but pharmacologically distinct (lower efficacy, slower receptor kinetics, absence of 5-HT1A activity).

Effect size: Not demonstrated. Both Phase 2 studies failed to show statistically significant efficacy versus placebo or standard of care.

Promising potential: Low. Development terminated. The compound serves as a pharmacological tool for distinguishing TAAR1 partial versus full agonism in the antipsychotic context.

Side-effect profile: Not adequately characterized in published data given early termination.

Overall validation: Low. The negative clinical outcomes, in contrast to ulotaront's positive Phase 2, suggest that TAAR1 partial agonism alone (without 5-HT1A co-agonism) may be insufficient for antipsychotic efficacy. The slower association kinetics and lower efficacy at TAAR1 may also contribute to the differential outcome [7].

Comparison to ulotaront: Ralmitaront is the most directly comparable compound to ulotaront, sharing the TAAR1 target but differing in agonist efficacy (partial versus full), receptor kinetics (slower versus faster association), and secondary pharmacology (absent versus present 5-HT1A activity). The clinical failure of ralmitaront where ulotaront showed Phase 2 efficacy suggests that the combination of full TAAR1 agonism and 5-HT1A co-agonism is important for clinical effect.

12.2 Xanomeline-trospium (Cobenfy, KarXT)

Mechanism: Dual M1/M4 muscarinic receptor agonism (xanomeline) combined with peripheral muscarinic antagonism (trospium chloride to mitigate peripheral cholinergic side effects). Approved by the FDA in September 2024 for the treatment of schizophrenia in adults [21, 22]. This is the first non-D2-based antipsychotic to receive FDA approval.

Development trajectory: Bristol Myers Squibb (through acquisition of Karuna Therapeutics) advanced xanomeline-trospium through two positive Phase 3 trials (EMERGENT-2 and EMERGENT-3) in acute schizophrenia, demonstrating statistically significant PANSS total score reduction versus placebo at 5 weeks (LS mean difference approximately minus 8.4 points, p less than 0.001 in EMERGENT-2) [21, 22].

Novelty: High. The muscarinic agonist mechanism is fundamentally distinct from both D2 antagonism and TAAR1 agonism. Xanomeline-trospium is the first approved antipsychotic that acts through cholinergic rather than dopaminergic or serotonergic targets.

Effect size: Robust. PANSS total score reduction of 20.6 points versus 12.2 points for placebo (difference approximately 8.4 points) in the pivotal trial, with effect sizes comparable to or exceeding those of second-generation antipsychotics [21].

Promising potential: High. FDA-approved and commercially available. Represents a validated non-D2 mechanism for antipsychotic therapy. Ongoing real-world evidence and long-term safety data will further define the therapeutic

positioning.

Side-effect profile: The principal adverse events are cholinergic in nature: nausea, indigestion, constipation, vomiting, hypertension, abdominal pain, diarrhea, tachycardia, dizziness, and gastroesophageal reflux disease [21, 22]. Hepatic enzyme elevation has been reported, and the compound is contraindicated in patients with hepatic impairment. The side-effect profile is distinct from D2 antagonists (no extrapyramidal symptoms, no tardive dyskinesia, no hyperprolactinemia) but introduces a cholinergic adverse-event burden that may limit tolerability in some patients.

Overall validation: High. FDA approval on the basis of two positive Phase 3 trials establishes xanomeline-trospium as the highest-validated non-D2 antipsychotic and the clinical benchmark against which ulotaront and other non-dopaminergic approaches must be measured.

Comparison to ulotaront: Xanomeline-trospium has achieved what ulotaront has not: positive Phase 3 readouts and regulatory approval. The cholinergic mechanism (M1/M4 agonism) is fundamentally different from the monoamine-modulatory mechanism (TAAR1/5-HT1A agonism) of ulotaront. Ulotaront's Phase 2 safety profile (minimal metabolic effects, no movement disorder signal, no prolactin elevation) compares favorably to xanomeline-trospium's cholinergic adverse-event burden, but the comparison is moot without Phase 3 efficacy. The two compounds represent complementary validation of the principle that antipsychotic efficacy is achievable without D2 receptor blockade.

12.3 Lumateperone (Caplyta)

Mechanism: Multi-target agent with serotonin 5-HT_{2A} antagonism, low-occupancy dopamine D₂ receptor partial agonism/presynaptic agonism (estimated D₂ occupancy approximately 40 percent at therapeutic doses), dopamine and serotonin transporter inhibition, and glutamate receptor modulation [23]. FDA-approved for schizophrenia (2019) and depressive episodes of bipolar I and II disorder (2021).

Development trajectory: Intra-Cellular Therapies advanced lumateperone through multiple positive Phase 3 trials in schizophrenia and bipolar depression. The compound is approved at a single dose of 42 mg once daily [23].

Novelty: Moderate. The compound incorporates 5-HT_{2A} antagonism and D₂ partial agonism, mechanisms shared with other atypical antipsychotics (aripiprazole, brexpiprazole), but the very low D₂ occupancy and the glutamate modulation represent incremental novelty within the D₂-engaging class.

Effect size: PANSS total score differences versus placebo in the pivotal schizophrenia trials were approximately 4 to 5 points, smaller than those observed with ulotaront in Phase 2 (7.5 points) and with xanomeline-trospium (8.4 points) [23].

Promising potential: Moderate. The compound is approved and commercially available. Its positioning is more in the tolerability-optimized atypical antipsychotic space than in the non-D₂ mechanistic space occupied by ulotaront and xanomeline-trospium.

Side-effect profile: Favorable relative to most atypical antipsychotics. Low rates of weight gain, metabolic effects, and extrapyramidal symptoms at the approved dose. Somnolence and sedation are the most common adverse events [23].

Overall validation: Moderate to high. FDA-approved for two indications with multiple positive Phase 3 trials.

Comparison to ulotaront: Lumateperone occupies a middle ground between conventional atypical antipsychotics (which it resembles in target class) and non-D₂ agents (from which it differs by retaining partial D₂ engagement). Ulotaront's complete absence of D₂ engagement is a more fundamental mechanistic departure. Lumateperone's approved status and favorable tolerability profile represent a higher level of clinical validation, but its smaller effect sizes and retained D₂ activity make it a less innovative comparator.

12.4 Emraclidine (CVL-231)

Mechanism: Selective positive allosteric modulator (PAM) of the muscarinic M₄ receptor. Unlike xanomeline, emraclidine acts at a single muscarinic subtype (M₄) through allosteric modulation rather than orthosteric agonism, theoretically minimizing peripheral cholinergic adverse effects and preserving the spatiotemporal specificity of endogenous acetylcholine signaling [24].

Development trajectory: Cerevel Therapeutics (acquired by AbbVie in 2024) advanced emraclidine through a positive Phase 1b trial in schizophrenia and into Phase 2 development. In August 2024, AbbVie reported that the Phase 2 EMPOWER-1 trial did not meet its primary endpoint of PANSS total score reduction versus placebo [24].

Novelty: High. The M4 PAM mechanism is the most mechanistically selective of the muscarinic approaches and represents a distinct strategy from both M1/M4 orthosteric agonism (xanomeline-trospium) and TAAR1 agonism (ulotaront).

Effect size: Phase 1b signals were promising; the Phase 2 trial was negative.

Promising potential: Low to moderate. The Phase 2 failure has reduced confidence in the M4 PAM approach as a standalone antipsychotic mechanism, although the mechanism remains of interest in combination strategies.

Side-effect profile: Phase 1b data suggested good tolerability with fewer cholinergic adverse events than xanomeline-trospium, consistent with the allosteric and M4-selective mechanism.

Overall validation: Low. Phase 2 negative readout, similar to ulotaront's Phase 3 negative readouts. The compound is not approved.

Comparison to ulotaront: Emraclidine and ulotaront share the trajectory of positive early-phase signals followed by negative later-phase readouts. Both represent novel non-D2 mechanisms that have struggled to replicate early efficacy signals in larger, definitive trials. The parallel failures raise questions about the role of placebo response, trial design, and patient selection in schizophrenia drug development, independent of the specific mechanism.

12.5 Cariprazine (Vraylar)

Mechanism: Dopamine D3-preferring partial agonist with D2 partial agonism and 5-HT_{1A} partial agonism [25]. FDA-approved for schizophrenia, bipolar mania, and bipolar depression. The D3 preference and partial agonism distinguish cariprazine from pure D2 antagonists and from the full D2 partial agonists (aripiprazole, brexpiprazole).

Development trajectory: AbbVie (originally Gedeon Richter/Allergan) advanced cariprazine through multiple positive Phase 3 trials. The compound is approved and commercially established at doses of 1.5 to 6 mg/day [25]. A landmark study demonstrated that cariprazine is the only approved antipsychotic with evidence of efficacy specifically for predominant negative symptoms of schizophrenia in a head-to-head comparison with risperidone (RGH-188-005 trial) [25].

Novelty: Low to moderate. The D3 preference is mechanistically incremental within the D2-engaging antipsychotic class.

Effect size: Standard antipsychotic effect sizes for positive symptoms. For negative symptoms, the head-to-head versus risperidone study demonstrated a statistically significant 2-point superiority on the PANSS factor score for negative symptoms at 26 weeks [25].

Promising potential: Moderate to high. The compound is approved and commercially available with a unique negative symptom positioning.

Side-effect profile: Akathisia is the principal adverse event (approximately 9 to 14 percent), reflecting the D2 partial agonism mechanism. Weight gain is modest (approximately 1 kg mean gain). Hyperprolactinemia is uncommon given the D2 partial agonism, but the compound is not free of D2-mediated adverse effects [25].

Overall validation: High. FDA-approved for three indications with positive Phase 3 trials.

Comparison to ulotaront: Cariprazine represents the D2-engaging comparator with the strongest negative symptom evidence. Ulotaront's Phase 2 negative symptom signal (BNSS effect size 0.48) is numerically larger than cariprazine's negative symptom effect in the head-to-head risperidone study, though the comparison is cross-study and methodologically indirect. Ulotaront's complete absence of D2-mediated adverse effects (akathisia, extrapyramidal symptoms) represents a tolerability advantage, contingent on achieving Phase 3 efficacy.

12.6 Comparator summary

The five comparator compounds span the spectrum of non-D2 and mechanistically novel approaches to antipsychotic pharmacology. **Xanomeline-trospium** (Cobenfy) is the clinical benchmark as the only FDA-approved non-D2 antipsychotic, with robust Phase 3 efficacy and a cholinergic adverse-event profile that creates a tolerabil-

ity niche. **Lumateperone** (Caplyta) is approved with favorable tolerability but retains partial D2 engagement and produces smaller effect sizes. **Cariprazine** (Vraylar) is the D2-class agent with the strongest negative symptom evidence but carries D2-associated adverse events (akathisia). **Ralmitaront** is the most direct TAAR1 comparator and failed in Phase 2, suggesting that full TAAR1 agonism plus 5-HT1A co-agonism may be necessary for the class mechanism. **Emraclidine** represents the most selective muscarinic approach (M4 PAM) and failed in Phase 2, mirroring ulotaront's Phase 3 difficulties.

Ulotaront occupies a unique but unvalidated position in this landscape: it is the only TAAR1 agonist with Phase 2 efficacy in schizophrenia, the only compound to demonstrate improvement across positive, negative, depressive, and global symptom domains with no metabolic, endocrine, or movement disorder signal, and the compound with the most favorable Phase 2 safety profile among the comparators. Its principal limitation is the failure to replicate Phase 2 efficacy in Phase 3. The ongoing development in anxiety and depression reflects the broader TAAR1/5-HT1A pharmacological potential beyond psychosis, and the outcome of those programs will substantially shape the future assessment of ulotaront's clinical positioning.

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