

RESEARCH MONOGRAPH . COMPOUND PROFILE

Aticaprant

A potent, orally bioavailable aminobenzyloxyarylamide kappa-opioid receptor antagonist developed at Eli Lilly and advanced through Phase 3 clinical evaluation for adjunctive treatment of major depressive disorder with anhedonia, distinguished from earlier KOR antagonists by favorable drug-like properties, short-acting receptor blockade, and a well-characterized safety profile.

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ABSTRACT

Aticaprant (LY-2456302, CERC-501, JNJ-67953964) is a potent, selective, orally bioavailable antagonist of the kappa-opioid receptor (KOR) with a binding affinity (K_i) of 0.81 nM, approximately 30-fold selectivity over the mu-opioid receptor (K_i = 24.0 nM), and approximately 190-fold selectivity over the delta-opioid receptor (K_i = 155 nM). The compound belongs to the aminobenzyloxyarylamide chemical class and was designed at Eli Lilly Research Laboratories as a clinically viable therapeutic targeting the endogenous dynorphin/KOR neuromodulatory system, a pathway implicated in the pathophysiology of stress-induced anhedonia, dysphoria, and addictive behaviors. In contrast to earlier KOR antagonists such as JDTic and nor-binaltorphimine, which exhibit ultra-long-duration receptor inactivation persisting for weeks after a single dose, aticaprant produces short-acting, reversible KOR blockade with an elimination half-life of 30 to 40 hours, enabling conventional once-daily oral dosing and predictable pharmacokinetic management.

The preclinical pharmacology of aticaprant was characterized in the seminal Rorick-Kehn et al. (2014) report, which demonstrated that oral administration selectively and potently occupied central KOR in vivo (ED_{50} = 0.33 mg/kg) without evidence of mu- or delta-opioid receptor occupancy at doses up to 30 mg/kg. In rodent behavioral models, aticaprant produced antidepressant-like effects in the mouse forced swim test, enhanced the efficacy of imipramine and citalopram, reduced ethanol self-administration in alcohol-preferring (P) rats, and reversed unpredictable chronic

mild stress-induced anhedonia in C57BL/6J mice, as measured by sucrose preference, nest building, and forced swim endpoints. Positron emission tomography (PET) imaging in humans confirmed near-complete saturation of brain KOR at a 10 mg oral dose (94% receptor occupancy at 2.5 hours post-dose), with sustained occupancy (82% at 24 hours for a 25 mg dose), supporting the translational pharmacology from preclinical models to human central nervous system target engagement.

Clinical development of aticaprant has proceeded through multiple sponsors. Eli Lilly conducted the initial Phase 1 single- and multiple-ascending dose studies (Lowe et al. 2014), establishing safety, tolerability, and the absence of clinically significant interactions with ethanol. Cerecor Inc. acquired the compound in 2015 and initiated early clinical studies in mood and substance use disorders. Janssen Pharmaceuticals (Johnson and Johnson) acquired the compound in 2017 and advanced it through Phase 2 and Phase 3 programs for adjunctive treatment of major depressive disorder (MDD) in patients with inadequate response to selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs). The Phase 2 randomized, double-blind, placebo-controlled study (Jacobsen et al. 2024) in 181 participants with MDD and moderate-to-severe anhedonia demonstrated a statistically significant reduction of 2.1 points on the Montgomery-Asberg Depression Rating Scale (MADRS) for aticaprant 10 mg versus placebo ($p = 0.04$), with favorable tolerability and no new safety signals. However, the compound did not separate from placebo on secondary measures of anhedonia (Snaith-Hamilton Pleasure Scale), global illness severity (CGI-S), anxiety (HAM-A), or patient-reported depression outcomes.

Janssen subsequently initiated the VENTURA Phase 3 program comprising five pivotal trials in MDD with anhedonia. On 6 March 2025, Johnson and Johnson announced discontinuation of the VENTURA program due to insufficient efficacy in the target population, while noting that the compound remained safe and well tolerated with no new safety signals detected. The most common treatment-emergent adverse events in clinical trials were headache (11.8% versus 7.1% placebo), diarrhea (8.2% versus 2.4%), nasopharyngitis (5.9% versus 2.4%), and pruritus (5.9% versus 0%). Johnson and Johnson has indicated that it will explore future development opportunities for aticaprant in other areas of high unmet need. The compound is not approved by any regulatory authority for any indication. This monograph reviews the chemistry, synthesis, receptor pharmacology, pharmacokinetics, preclinical and clinical evidence base, sourcing and quality considerations, reconstitution and handling, stack interactions, adverse-event profile, and a comparative assessment of five KOR antagonist candidates against aticaprant on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Aticaprant.

Development codes: LY-2456302 (Eli Lilly and Company), CERC-501 (Cerecor Inc.), JNJ-67953964 (Janssen Pharmaceuticals, Johnson and Johnson Innovative Medicine). The LY-2456302 code is the canonical identifier in the original preclinical and Phase 1 pharmacology literature. The CERC-501 code appears in early clinical development publications from the Cerecor period (2015 to 2017). The JNJ-67953964 code is the current sponsor identifier used in Phase 2 and Phase 3 clinical trial registrations and regulatory communications [1, 2].

Chemical Abstracts Service registry number: 1174130-61-0.

International Union of Pure and Applied Chemistry name: 4-[4-[[[(2S)-2-(3,5-dimethylphenyl)pyrrolidin-1-yl]methyl]phenoxy]-3-fluorobenzamide. The compound is the (2S)-enantiomer; the stereocenter at the pyrrolidine 2-position is the principal determinant of KOR selectivity and binding affinity.

SMILES	notation:	CC1=CC(=CC(C)=C1)
<chem>[C@@H]2CCCN2CC3=CC=C(OC4=CC=C(C(N)=O)C=C4F)C=C3.</chem>		

Other identifiers: UNII code DE4G8X55F5 (United States National Library of Medicine Substance Registration System).

1.2 Structural class and chemistry

Aticaprant is an aminobenzyloxyarylamide, a synthetic small-molecule scaffold designed through structure-activity relationship optimization at Eli Lilly Research Laboratories for selective KOR antagonism with favorable oral bioavailability and CNS penetration. The structural class is distinct from the morphinan-derived KOR antagonists (nor-binaltorphimine, GNTI, 5'-guanidinonaltrindole) and from the trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (JDTic) class. The non-opioid scaffold was deliberately selected to avoid mu-opioid receptor agonism or antagonism at clinical doses and to eliminate the ultra-long-duration receptor inactivation characteristic of the JDTic and nor-BNI chemical classes [1, 3].

Molecular formula: C₂₆H₂₇FN₂O₂.

Molecular weight: 418.50 g/mol.

Physical properties: White to off-white solid. Soluble in dimethyl sulfoxide (DMSO) and organic solvents; limited aqueous solubility as the free base. The compound is supplied commercially as the free base for research applications. Melting point data are reported in proprietary pharmaceutical characterization dossiers and are not published in the open literature.

Stereochemistry: Aticaprant contains one stereocenter at carbon 2 of the pyrrolidine ring. The compound is supplied and characterized as the single (2S)-enantiomer. The (2S)-configuration is essential for the high-affinity KOR binding; the (2R)-enantiomer exhibits substantially reduced KOR affinity in radioligand displacement assays. Investigators acquiring research-grade aticaprant should confirm enantiomeric purity by chiral high-performance liquid chromatography.

1.3 Synthesis

The published synthesis of aticaprant proceeds through a convergent strategy involving the preparation of three principal fragments: the 3,5-dimethylphenyl-substituted (2S)-pyrrolidine, the 4-hydroxybenzyl linker, and the 3-fluoro-4-aminocarbonylphenyl ether. The pyrrolidine fragment is prepared by asymmetric synthesis or resolution to provide the (2S)-enantiomer in high optical purity. The key bond-forming step is the reductive amination coupling of the pyrrolidine nitrogen with the benzaldehyde linker fragment, followed by Williamson ether synthesis or copper-catalyzed coupling to install the diaryl ether bond. The primary amide is introduced at the benzamide terminus. Purification is by column chromatography and recrystallization. The compound is characterized by proton and carbon-13 nuclear magnetic resonance spectroscopy, high-resolution mass spectrometry, and high-performance liquid chromatography. The synthetic route has been optimized for kilogram-scale production by Eli Lilly and subsequently by Janssen for clinical supply. The detailed process chemistry has not been published in the peer-reviewed literature; the synthetic approach is described in patent applications [3, 4].

2. Abstract

Aticaprant (LY-2456302, CERC-501, JNJ-67953964) is a potent, selective, short-acting antagonist of the kappa-opioid receptor (KOR) with a binding affinity K_i of 0.81 nM and approximately 30-fold selectivity over the mu-opioid receptor (MOR) and approximately 190-fold selectivity over the delta-opioid receptor (DOR) [1]. The compound was designed at Eli Lilly Research Laboratories as a non-morphinan, orally bioavailable small molecule targeting the endogenous dynorphin/KOR neuromodulatory system, a pathway that is activated during chronic stress exposure and that suppresses mesolimbic dopaminergic neurotransmission, producing anhedonia, dysphoria, and aversion. The KOR antagonist mechanism disinhibits dopaminergic tone and restores reward sensitivity, providing the therapeutic rationale for application in major depressive disorder, particularly in the anhedonic subtype, and in substance use disorders.

The preclinical pharmacology, characterized in the Rorick-Kehn et al. (2014) report from Eli Lilly, demonstrated that aticaprant selectively occupied central KOR in vivo (ED_{50} = 0.33 mg/kg oral) without mu- or delta-opioid receptor occupancy at doses 100-fold higher, produced antidepressant-like effects in the mouse forced swim test, potentiated the effects of conventional antidepressants, and reduced ethanol self-administration in alcohol-preferring rats [1]. Subsequent preclinical work by Browne et al. (2020) demonstrated reversal of unpredictable chronic mild stress-induced anhedonia in male C57BL/6J mice, with restoration of sucrose preference, nest building, and adaptive coping behavior following 11 days of aticaprant administration at 10 mg/kg [5]. Preclinical evidence in alcohol dependence models (Anderson et al. 2022) showed that aticaprant combined with naltrexone prevented alcohol relapse drinking in dependent rats, with aticaprant alone reversing anxiety-like behavior during alcohol withdrawal and reducing stress-induced reinstatement of alcohol seeking [6].

Clinical development has been conducted sequentially by Eli Lilly (Phase 1), Cerecor (early clinical), and Janssen Pharmaceuticals (Phase 2 and Phase 3). The Phase 1 single- and multiple-ascending dose study in healthy volunteers (Lowe et al. 2014) established safety, tolerability, and favorable pharmacokinetic properties, with no clinically significant ethanol interaction [2]. The PET receptor occupancy study demonstrated that a single 10 mg oral dose produced 94% KOR occupancy in

human brain at 2.5 hours post-dose [7]. The Phase 2 study (Jacobsen et al. 2024) in 181 adults with MDD and inadequate SSRI/SNRI response demonstrated a statistically significant 2.1-point MADRS improvement over placebo with adjunctive aticaprant 10 mg ($p = 0.04$), though secondary anhedonia endpoints did not reach significance [8]. The Phase 3 VENTURA program (five trials) was discontinued in March 2025 due to insufficient efficacy in the target MDD population, despite a favorable safety profile [9].

The compound is not approved by any regulatory authority. Johnson and Johnson has indicated it will explore development in other therapeutic areas. The most common adverse events in clinical trials were headache, diarrhea, nasopharyngitis, and pruritus, all at modest frequencies without serious safety signals. This monograph documents the chemistry, synthesis, receptor pharmacology, pharmacokinetics, preclinical evidence, clinical trial results, sourcing, reconstitution, drug interactions, adverse events, and a comparative assessment of five KOR antagonist candidates against aticaprant.

3. Discovery and Development History

3.1 Origin

Aticaprant was synthesized at Eli Lilly Research Laboratories in Indianapolis, Indiana, as part of a structure-activity relationship program to identify selective KOR antagonists with drug-like properties suitable for clinical development in mood and addictive disorders. The program was motivated by the accumulating preclinical evidence that the endogenous dynorphin/KOR system is activated by chronic stress and mediates the anhedonic, dysphoric, and aversive components of the stress response through suppression of mesolimbic and mesocortical dopaminergic neurotransmission [1, 3]. Earlier KOR antagonists, including nor-binaltorphimine (nor-BNI, a morphinan) and JDtic (a trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine), demonstrated the therapeutic potential of KOR blockade in preclinical models but were unsuitable for clinical development due to ultra-long-duration receptor inactivation (weeks to months after a single dose), complex pharmacokinetics, and, in the case of JDtic, cardiac safety concerns that led to termination of its clinical program after a single-dose Phase 1 study [10, 11].

The Eli Lilly team adopted a non-opioid scaffold strategy, designing the aminobenzyloxyarylamide class to achieve high KOR affinity and selectivity without the morphinan core responsible for mu-opioid cross-reactivity and without the persistent receptor inactivation mechanism of the JDtic class. The compound was first patented in 2009, and the first scientific disclosure of LY-2456302 appeared in 2011 [1, 3].

3.2 Preclinical characterization at Eli Lilly

The seminal Rorick-Kehn et al. (2014) publication in *Neuropharmacology* reported the complete in vitro and in vivo pharmacological profile of LY-2456302, including radioligand binding ($K_i = 0.81$ nM at human KOR), selectivity panel (30-fold over MOR, 190-fold over DOR, and greater than 100-fold over a broad panel of non-opioid receptors and ion channels), in vivo receptor occupancy by ex vivo autoradiography ($ED_{50} = 0.33$ mg/kg oral in rat), pharmacokinetics in rat (oral bioavailability approximately 25%, T_{max} 1 to 2 hours), and behavioral pharmacology in the mouse

forced swim test, the rat ethanol self-administration paradigm, and a drug combination study with imipramine and citalopram [1]. The compound was advanced to IND-enabling studies on the basis of this profile.

3.3 Phase 1 development at Eli Lilly

Lowe et al. (2014) published the Phase 1 single- and multiple-ascending dose study and ethanol drug-drug interaction study in healthy volunteers in the Journal of Clinical Pharmacology [2]. Single doses from 0.5 mg to 120 mg and multiple doses from 2 mg to 60 mg daily for 14 days were evaluated. The compound was well tolerated across all dose levels, with no clinically significant adverse events, no dose-limiting toxicities, and no clinically meaningful effects on vital signs, electrocardiography, or laboratory parameters. The ethanol interaction arm demonstrated no additive impairment on cognitive or psychomotor assessments when aticaprant was co-administered with ethanol, a finding of practical importance for a compound intended for use in populations with comorbid alcohol use [2].

3.4 Transfer to Cerecor

In February 2015, Cerecor Inc. acquired the worldwide rights to LY-2456302 from Eli Lilly and redesignated the compound CERC-501. Cerecor initiated clinical studies in smoking cessation and in cocaine use disorder. A Phase 2 proof-of-concept study in smoking cessation did not demonstrate efficacy [12]. A Phase 1b study in cocaine use disorder was conducted but did not advance to Phase 2. Cerecor also initiated the pupillometry biomarker study (Jacobson et al. 2016) establishing pupil dilation as a translational pharmacodynamic biomarker for KOR antagonism in both rat and human, confirming that aticaprant produced dose-dependent pupil dilation consistent with KOR blockade [13].

3.5 Transfer to Janssen Pharmaceuticals

In August 2017, Cerecor sold its rights to aticaprant to Janssen Pharmaceuticals (Johnson and Johnson), which redesignated the compound JNJ-67953964. Janssen repositioned the development program toward adjunctive treatment of major depressive disorder in patients with anhedonia and inadequate response to first-line antidepressant therapy. This repositioning was informed by the mechanistic ratio-

nale that KOR antagonism would specifically address the anhedonic and motivational deficit component of depression, which is poorly served by SSRI/SNRI monotherapy [8, 14].

3.6 Phase 2 development at Janssen

Janssen conducted a randomized, double-blind, placebo-controlled Phase 2 study (NCT03559192) evaluating aticaprant 10 mg daily as adjunctive therapy to ongoing SSRI/SNRI treatment in 181 adults with MDD and moderate-to-severe anhedonia (Snaith-Hamilton Pleasure Scale score of 20 or higher). The study met its primary endpoint, demonstrating a statistically significant 2.1-point improvement in MADRS total score for aticaprant versus placebo ($p = 0.04$) at 6 weeks. However, the secondary endpoints, including the SHAPS anhedonia measure, the Clinical Global Impression-Severity scale, the Hamilton Anxiety Rating Scale, and the Symptoms of Major Depressive Disorder Scale, did not separate from placebo. The results were published by Jacobsen et al. (2024) in *Neuropsychopharmacology* [8].

3.7 Phase 3 VENTURA program and discontinuation

On the basis of the Phase 2 primary endpoint result, Janssen initiated the VENTURA Phase 3 program comprising five pivotal trials (VENTURA-1 through VENTURA-7, with select trial designations) evaluating aticaprant 10 mg as adjunctive therapy in adults with MDD and moderate-to-severe anhedonia with inadequate SSRI/SNRI response. On 6 March 2025, Johnson and Johnson issued a press release announcing discontinuation of the VENTURA program due to insufficient efficacy in the target population [9]. The company stated that aticaprant was safe and well tolerated throughout the program, with no new safety signals detected, and indicated that it would explore future development opportunities in other therapeutic areas. Full data from the VENTURA program were stated to be forthcoming at a future medical meeting.

The discontinuation of the VENTURA program occurred approximately two months after Neumora Therapeutics announced the failure of its KOR antagonist navacaprant (BTRX-335140) in a Phase 3 MDD trial in January 2025 [15]. The sequential Phase 3 failures of two mechanistically related compounds have substantially dampened enthusiasm for KOR antagonism as a monotherapy or adjunctive therapy strategy in MDD, though the mechanism retains preclinical support in stress-related and substance use disorder models.

4. Mechanism of Action

Aticaprant is a single-target ligand with high selectivity for the kappa-opioid receptor. Its therapeutic mechanism operates through blockade of the endogenous dynorphin/KOR neuromodulatory system, which tonically suppresses mesolimbic dopaminergic neurotransmission during and after chronic stress exposure.

4.1 Kappa-opioid receptor pharmacology

The kappa-opioid receptor (KOR, also designated OPRK1) is a G protein-coupled receptor of the opioid receptor family, coupled to inhibitory Gi/Go proteins. It is expressed at high density in the ventral tegmental area, nucleus accumbens, dorsal striatum, prefrontal cortex, hippocampus, amygdala, and hypothalamus, as well as on peripheral sensory neurons and immune cells. The endogenous ligand is dynorphin, a peptide derived from the prodynorphin gene, which is released during stress, inflammation, and pain states [16].

KOR activation produces several downstream effects: inhibition of adenylyl cyclase and reduction of cyclic AMP, activation of G protein-coupled inwardly rectifying potassium (GIRK) channels producing neuronal hyperpolarization, inhibition of voltage-gated calcium channels reducing neurotransmitter release, and activation of beta-arrestin-2-dependent signaling cascades that include p38 mitogen-activated protein kinase phosphorylation. In mesolimbic dopamine neurons, KOR activation directly suppresses dopamine release in the nucleus accumbens, producing anhedonia and dysphoria. In the prefrontal cortex, KOR activation impairs working memory and cognitive flexibility. In the amygdala and hippocampus, KOR activation modulates fear conditioning and stress memory consolidation [16, 17].

4.2 Mechanism of KOR antagonism by aticaprant

Aticaprant binds the KOR at the orthosteric binding site with a K_i of 0.81 nM, competing with dynorphin and with KOR agonists (U-50,488H, salvinorin A) for receptor occupancy. The antagonism is competitive and reversible, in contrast to the pseudo-irreversible or wash-resistant antagonism produced by nor-BNI and JDTic, which bind at or near the orthosteric site but produce persistent receptor inactivation.

tion through a mechanism involving c-Jun N-terminal kinase (JNK) signaling rather than through slow dissociation kinetics [11, 18]. The reversible, competitive mechanism of aticaprant produces pharmacodynamic effects that are proportional to plasma concentration and that dissipate with drug elimination, enabling conventional once-daily dosing and dose titration.

The selectivity of aticaprant is approximately 30-fold over the mu-opioid receptor (MOR, $K_i = 24.0$ nM) and approximately 190-fold over the delta-opioid receptor (DOR, $K_i = 155$ nM). In vivo, oral administration at doses up to 30 mg/kg in rat produced no measurable occupancy at MOR or DOR by ex vivo autoradiography, confirming functional selectivity at therapeutically relevant doses [1]. The absence of MOR activity is operationally important: it means that aticaprant does not produce the euphoria, respiratory depression, physical dependence, or opioid withdrawal precipitation associated with MOR agonism or antagonism, and it does not interfere with the analgesic efficacy of mu-opioid analgesics at clinical doses.

4.3 Downstream consequences of KOR blockade

The principal downstream consequence of KOR antagonism in the mesolimbic dopamine system is disinhibition of dopaminergic neurotransmission. By blocking the tonic inhibitory effect of dynorphin on ventral tegmental area dopamine neurons and on dopamine terminals in the nucleus accumbens, aticaprant restores dopamine release in reward-processing circuits that are suppressed during chronic stress. This disinhibition is the mechanistic basis for the anti-anhedonic and antidepressant-like effects observed in preclinical models and the rationale for clinical application in MDD with anhedonia [5, 16, 17].

Additional downstream effects of KOR blockade include modulation of serotonergic neurotransmission (KOR is expressed on dorsal raphe serotonin neurons and blockade may enhance serotonergic output, providing a mechanistic rationale for synergy with SSRI/SNRI therapy), reduction of stress-induced hypothalamic-pituitary-adrenal axis activation, modulation of inflammatory signaling through KOR expressed on immune cells, and reduction of stress-induced aversion learning [16].

4.4 Functional selectivity considerations

Aticaprant is a competitive antagonist that blocks both G protein-dependent and beta-arrestin-dependent KOR signaling. The compound does not exhibit functionally selective (biased) antagonism; it blocks all downstream KOR signaling pathways equipotently at concentrations achieving receptor occupancy. This distinguishes the compound from biased KOR ligands that preferentially activate or block specific signaling cascades. The clinical relevance of biased versus unbiased KOR antagonism remains an active area of investigation; unbiased antagonism may be advantageous for full blockade of the dynorphin-mediated stress response, while biased approaches might offer pathway-selective modulation with potentially different therapeutic or side-effect profiles [17, 18].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Aticaprant is rapidly absorbed after oral administration. The time to peak plasma concentration (T_{max}) is 1 to 2 hours in both preclinical species (rat) and in healthy human volunteers [1, 2]. Oral bioavailability is approximately 25% in both rat and human, with the relatively modest bioavailability attributable to first-pass hepatic metabolism. Circulating plasma concentrations increase proportionally with dose over the studied range (0.5 mg to 120 mg single dose in Phase 1), indicating linear pharmacokinetics across the clinically relevant dose range [2]. Food effects on absorption have not been reported in the published literature.

5.2 Distribution

Aticaprant penetrates the blood-brain barrier effectively, as demonstrated by PET receptor occupancy studies and by ex vivo autoradiography in rat [1, 7]. The compound achieves near-complete KOR occupancy in human brain at a 10 mg oral dose (94% occupancy at 2.5 hours post-dose), confirming robust central nervous system penetration at clinical doses. Occupancy at lower doses is dose-dependent: 35% for 0.5 mg and progressively higher with increasing dose. At 24 hours post-dose, receptor occupancy remained substantial (82% for 25 mg), consistent with the long elimination half-life and supporting once-daily dosing [7].

Volume of distribution and plasma protein binding values have not been reported in the published peer-reviewed literature. The PET data and the in vivo receptor occupancy pharmacology indicate that the compound distributes extensively to brain tissue at concentrations sufficient for near-complete target engagement.

5.3 Metabolism

The specific cytochrome P450 enzymes responsible for aticaprant metabolism have not been fully characterized in the published peer-reviewed literature. The modest oral bioavailability (25%) indicates substantial first-pass hepatic metabolism. Phase 1 clinical trial data did not identify clinically significant metabolic drug-drug interactions at the studied doses [2]. The ethanol interaction study demonstrated no pharmacokinetic or pharmacodynamic interaction between aticaprant and ethanol, suggesting that the principal metabolic pathways do not overlap substantially with ethanol metabolism [2].

5.4 Elimination

The terminal elimination half-life of aticaprant is 30 to 40 hours in healthy human subjects, substantially longer than the 1 to 2 hour absorption phase [2]. Steady-state plasma concentrations are reached after approximately 6 to 8 days of once-daily dosing, consistent with the long elimination half-life [2, 8]. The specific elimination pathways (renal versus hepatic, proportion of unchanged drug in urine) have not been fully reported in the published peer-reviewed literature.

5.5 Routes of administration

Aticaprant has been administered exclusively by the oral route in all published clinical studies. The Phase 2 and Phase 3 programs used a 10 mg once-daily oral dose [8, 9]. The Phase 1 program evaluated single oral doses from 0.5 mg to 120 mg and multiple oral doses from 2 mg to 60 mg daily [2]. No intravenous, intramuscular, or subcutaneous formulations have been reported. For preclinical research, the compound is typically administered by oral gavage or by intraperitoneal injection in rodent models [1, 5].

5.6 Special populations

Pharmacokinetic data in special populations (hepatic impairment, renal impairment, elderly, pediatric) have not been reported in the published peer-reviewed literature. The Phase 3 VENTURA program included adult and elderly participants, but pharmacokinetic subgroup analyses have not been published. The compound has not been studied in pregnant or lactating subjects.

6. Preclinical Pharmacology

6.1 In vitro receptor pharmacology

The in vitro pharmacological profile of aticaprant was characterized by Rorick-Kehn et al. (2014) [1]. Binding affinity at the human KOR was $K_i = 0.81$ nM by [3 H]-diprenorphine displacement. Selectivity over MOR was approximately 30-fold ($K_i = 24.0$ nM) and over DOR approximately 190-fold ($K_i = 155$ nM). The compound was inactive (K_i greater than 10 micromolar) at a broad panel of non-opioid receptors, ion channels, and transporters, including serotonin receptors (5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT₃), dopamine receptors (D₁ through D₅), adrenergic receptors (α -1, α -2, β), muscarinic receptors, GABA-A receptors, NMDA receptors, and monoamine transporters (SERT, NET, DAT). This broad selectivity panel distinguishes aticaprant from older KOR tools (nor-BNI, which has significant MOR and DOR activity) and from the endogenous dynorphin peptides [1].

Functional antagonism was confirmed in GTP γ S binding assays: aticaprant produced rightward shifts in the concentration-response curves for the KOR agonist U-50,488H with a pA_2 consistent with competitive antagonism. The compound did not exhibit partial agonist activity at KOR in any assay system tested, confirming a pure antagonist profile [1].

6.2 In vivo receptor occupancy

Ex vivo autoradiography in rat demonstrated that oral aticaprant produced dose-dependent occupancy of central KOR with an ED₅₀ of 0.33 mg/kg. At doses up to 30 mg/kg (approximately 100-fold the ED₅₀), no measurable occupancy of MOR or DOR was observed, confirming in vivo functional selectivity [1]. PET imaging in humans using the KOR-selective radiotracer [11 C]LY2795050 demonstrated that a single 10 mg oral dose of aticaprant produced 94% KOR occupancy at 2.5 hours post-dose, while a 0.5 mg dose produced 35% occupancy. At 24 hours post-dose, KOR occupancy was 82% for a 25 mg dose and 19% for a 0.5 mg dose, consistent with sustained target engagement over the dosing interval [7].

6.3 Behavioral pharmacology in mood disorder models

Aticaprant produced antidepressant-like effects in the mouse forced swim test (reduced immobility time) and enhanced the efficacy of the conventional antidepressants imipramine and citalopram in the same paradigm, consistent with a synergistic interaction between KOR blockade and monoamine reuptake inhibition [1]. The forced swim enhancement provided the preclinical rationale for the adjunctive (rather than monotherapy) clinical development strategy.

Browne et al. (2020) evaluated aticaprant in the unpredictable chronic mild stress (UCMS) model in male C57BL/6J mice, a paradigm that produces an anhedonia-like phenotype measured by reduced sucrose preference, impaired nesting behavior, and increased immobility in the forced swim test. Following 4 weeks of UCMS exposure, daily aticaprant treatment (10 mg/kg intraperitoneal for 11 days) reversed deficits in sucrose preference (the primary anhedonia measure), nesting behavior (a marker of self-care and motivated behavior), and forced swim immobility (adaptive coping). Aticaprant did not reverse UCMS-induced anxiety-like behavior (light-dark test) or social interaction deficits, suggesting that the anti-anhedonic and antidepressant effects are mechanistically separable from the anxiolytic and pro-social domains [5].

6.4 Behavioral pharmacology in substance use disorder models

Rorick-Kehn et al. (2014) demonstrated that aticaprant reduced ethanol self-administration in alcohol-preferring (P) rats, a genetically selected line that voluntarily consumes ethanol at levels producing pharmacologically relevant blood alcohol concentrations. The reduction was sustained over 4 days of repeated dosing without evidence of tolerance, supporting the potential for chronic use in alcohol use disorder [1].

Anderson et al. (2022) extended the alcohol dependence pharmacology, demonstrating that aticaprant reversed anxiety-like behavior during alcohol withdrawal in dependent rats, reduced escalation of ethanol intake following prolonged intermittent access (a model of compulsive drinking), and selectively decreased stress-induced reinstatement of alcohol seeking. Combination of aticaprant with naltrexone (a non-selective opioid antagonist approved for alcohol use disorder) produced

complementary effects: naltrexone reduced cue-induced reinstatement while aticaprant reduced stress-induced reinstatement, and the combination prevented alcohol relapse drinking across multiple reinstatement modalities [6].

Clinical studies of aticaprant in substance use disorders (smoking cessation, cocaine use disorder) conducted during the Cerecor development period did not demonstrate efficacy. The smoking cessation Phase 2 study did not meet its primary endpoint, and the cocaine use disorder program was discontinued after Phase 1b [12].

6.5 Translational biomarkers

Jacobson et al. (2016) established pupil dilation (mydriasis) as a translational pharmacodynamic biomarker for KOR antagonism, demonstrating that aticaprant produced dose-dependent pupil dilation in both rat and human, with the magnitude of dilation correlating with predicted KOR occupancy. This biomarker was proposed as a non-invasive measure of KOR target engagement for use in clinical dose-finding studies [13].

7. Clinical Evidence Base

7.1 Phase 1 clinical pharmacology

The Lowe et al. (2014) Phase 1 study evaluated single-ascending doses (0.5 to 120 mg) and multiple-ascending doses (2 to 60 mg daily for 14 days) in healthy volunteers. Aticaprant was well tolerated across all dose levels with no serious adverse events, no dose-limiting toxicities, and no clinically significant changes in vital signs, electrocardiography, or clinical laboratory parameters [2].

The ethanol drug-drug interaction arm was included because the anticipated clinical populations (depression, substance use disorders) have high rates of comorbid alcohol consumption. Co-administration of aticaprant with ethanol produced no pharmacokinetic interaction (no change in aticaprant or ethanol plasma concentrations) and no pharmacodynamic interaction on cognitive or psychomotor assessments (no additive impairment beyond what ethanol alone produced). This finding was interpreted as supporting the real-world tolerability and acceptability of the compound [2].

7.2 PET receptor occupancy studies

PET imaging using the KOR-selective radiotracer [11C]LY2795050 was conducted in healthy volunteers to establish the dose-occupancy relationship. At 2.5 hours post-dose, KOR occupancy was 35% (0.5 mg dose), approximately 73% (2 mg dose, estimated from dose-response curve), and 94% (10 mg dose). The 10 mg dose was selected for Phase 2 clinical development on the basis of near-complete receptor occupancy at this dose level [7].

7.3 Phase 2 study in major depressive disorder

The Jacobsen et al. (2024) Phase 2 study (NCT03559192) was a randomized, double-blind, placebo-controlled study of aticaprant 10 mg once daily as adjunctive therapy to ongoing SSRI/SNRI treatment in 181 adults with MDD and moderate-to-severe anhedonia (defined as SHAPS score of 20 or higher) who had an inadequate response to their current antidepressant [8].

Primary endpoint: Change from baseline in MADRS total score at week 6. Aticaprant demonstrated a statistically significant improvement of 2.1 points versus placebo on the MADRS ($p = 0.04$).

Secondary endpoints: The Snaith-Hamilton Pleasure Scale (SHAPS), the primary measure of anhedonia, did not separate from placebo. The Clinical Global Impression-Severity scale (CGI-S), the Hamilton Anxiety Rating Scale (HAM-A), and the Symptoms of Major Depressive Disorder Scale (SMDDS, a patient-reported outcome) also did not separate from placebo.

Safety and tolerability: Only one participant (1.2%) in each treatment arm discontinued due to adverse events. The most common treatment-emergent adverse events in the aticaprant arm were headache (11.8% versus 7.1% placebo), diarrhea (8.2% versus 2.4%), nasopharyngitis (5.9% versus 2.4%), and pruritus (5.9% versus 0%). No serious adverse events were attributed to study drug. No clinically significant changes in vital signs, electrocardiographic parameters, or laboratory values were observed [8].

Interpretation: The Phase 2 study demonstrated a statistically significant but clinically modest effect on the primary depression rating scale, with the effect size insufficient to move secondary measures of anhedonia, global severity, anxiety, or patient-reported outcomes. The discrepancy between the primary MADRS signal and the absent SHAPS signal was notable, given that the study was specifically designed to test the anti-anhedonic hypothesis of KOR antagonism. Multiple interpretations were proposed: (a) the MADRS captures broader depressive symptomatology beyond anhedonia; (b) the SHAPS may lack sensitivity to the specific motivational and reward deficits addressed by KOR blockade; (c) the effect size may be too small to be detected on secondary measures; (d) the 6-week treatment duration may be insufficient for full anti-anhedonic effect [8, 14].

7.4 Phase 3 VENTURA program

Janssen initiated the VENTURA Phase 3 program based on the Phase 2 primary endpoint result. The program comprised five trials evaluating aticaprant 10 mg as adjunctive therapy in adults with MDD and moderate-to-severe anhedonia with inadequate SSRI/SNRI response. Individual trial registrations included NCT05550532 (VENTURA-5, initiated September 2024), NCT05518149 (VENTURA-7, initiated June 2024), and additional trials registered on ClinicalTrials.gov.

On 6 March 2025, Johnson and Johnson announced discontinuation of the VENTURA program, stating: "Based on the totality of data from the VENTURA clinical development program, Johnson and Johnson has made the decision to discontinue the development of aticaprant as an adjunctive treatment for major depressive disorder (aMDD) due to insufficient efficacy in the target patient population" [9]. The company noted that aticaprant remained safe and well tolerated, with no new safety signals detected, and stated that full data from the VENTURA program would be presented at a future medical meeting.

7.5 Clinical studies in substance use disorders

Clinical studies of aticaprant in substance use disorders were conducted during the Cerecor development period (2015 to 2017). A Phase 2 proof-of-concept study in smoking cessation did not demonstrate efficacy [12]. A Phase 1b study in cocaine use disorder was conducted but did not advance to Phase 2. Development for alcoholism, cocaine use disorder, and nicotine withdrawal was discontinued as of the Janssen acquisition. The preclinical evidence in alcohol dependence models (Anderson et al. 2022) remains the strongest translational support for substance use disorder applications, but clinical development in this area has not been pursued by the current sponsor [6, 12].

7.6 Other investigational applications

Aticaprant has been described in preclinical literature and in clinical trial registry documents in connection with potential applications in anxiety disorders, post-traumatic stress disorder, and treatment-resistant depression. No published clinical trial results are available for these indications. The mechanism (KOR blockade addressing stress-induced anhedonia and dysphoria) provides a plausible rationale for these applications, but clinical data are limited to the MDD program [14].

8. Sourcing and Quality Verification

Aticaprant is not a marketed pharmaceutical product in any jurisdiction. The compound is available exclusively as a research-grade preparation from specialty chemical and pharmaceutical research suppliers.

Research-grade aticaprant is supplied by multiple vendors (MedChemExpress, Selleck Chemicals, Cayman Chemical, MedKoo Biosciences, GlpBio, TargetMol, BocSci, others) at greater than 98% purity by HPLC. Supply is in milligram to gram quantities as the free base. The compound is catalogued under CAS 1174130-61-0. Pricing is moderate for a research compound of this class, typically in the range of \$100 to \$500 per 50 mg to 100 mg depending on vendor, quantity, and purity grade.

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

- High-performance liquid chromatography area-percent purity (target: greater than 98%)
- Mass spectrometry confirmation of molecular weight (expected $[M+H]^+ = 419.21$ for $C_{26}H_{27}FN_2O_2$)
- Chiral HPLC confirmation of enantiomeric purity (target: greater than 99% enantiomeric excess of the (2S)-form)
- Proton nuclear magnetic resonance spectroscopy for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories (Janoshik Analytical, others) can provide independent confirmation of vendor certificates of analysis. Because aticaprant is not a marketed pharmaceutical, there is no pharmacopoeial reference standard; investigators should use vendor-supplied reference standards or request certificate-of-analysis data from the supplier.

9. Reconstitution and Handling

Aticaprant free base is a white to off-white solid with limited aqueous solubility. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions (10 to 100 mM), which are then diluted into aqueous assay buffers. Final DMSO concentration in assay media should be maintained below 0.1% to avoid solvent effects on biological systems.

For in vivo research applications in rodent models, aticaprant has been administered by oral gavage (dissolved or suspended in appropriate vehicles such as methylcellulose, polyethylene glycol 400, or cyclodextrin-based formulations) or by intraperitoneal injection (dissolved in DMSO with subsequent dilution into saline or other biocompatible vehicles) [1, 5].

Storage of the solid compound should be at -20 degrees Celsius, desiccated and protected from light. DMSO stock solutions should be aliquoted for single use and stored at -20 degrees Celsius. The compound is reported to be stable under recommended storage conditions for at least 2 years as the solid and for at least 6 months as frozen DMSO stocks, though stability data from multiple vendors vary and on-receipt verification is recommended.

Aqueous solutions at physiological pH may exhibit limited stability due to the amide functionality; investigators should prepare aqueous working solutions immediately before use or validate stability in their specific buffer system.

10. Stack Interactions and Combinations

Aticaprant interacts with several drug classes through its KOR pharmacology and through potential metabolic interactions. Investigators conducting research with aticaprant, especially in combination protocols, should consider the following:

Opioid analgesics (mu-opioid agonists): Aticaprant does not antagonize the mu-opioid receptor at clinical doses (30-fold selectivity), and co-administration with mu-opioid analgesics is not expected to reduce analgesic efficacy or precipitate opioid withdrawal. This is a meaningful distinction from non-selective opioid antagonists (naltrexone, naloxone) that block MOR at clinical doses and are contraindicated during opioid therapy. However, at supratherapeutic doses, aticaprant may begin to occupy MOR, and investigators should be aware of this theoretical risk in high-dose research protocols [1].

Non-selective opioid antagonists (naltrexone, naloxone): Combination with naltrexone has been investigated preclinically by Anderson et al. (2022) for alcohol use disorder, demonstrating complementary effects: naltrexone addressing cue-induced reinstatement through MOR blockade and aticaprant addressing stress-induced reinstatement through KOR blockade [6]. The combination is pharmacologically rational and has not produced additive adverse events in preclinical models.

SSRI and SNRI antidepressants: The Phase 2 and Phase 3 clinical programs evaluated aticaprant exclusively as adjunctive therapy with ongoing SSRI/SNRI treatment. No pharmacokinetic drug-drug interactions between aticaprant and SSRI/SNRI agents have been reported. The mechanistic rationale for the combination is that SSRI/SNRI therapy addresses serotonergic and noradrenergic deficits in depression while aticaprant addresses the dopaminergic/reward deficit component through KOR blockade [8].

Tricyclic antidepressants (imipramine, others): Preclinical data demonstrate that aticaprant potentiates the antidepressant-like effects of imipramine in the mouse forced swim test [1]. The clinical relevance of this interaction has not been evaluated.

Ethanol: The Phase 1 study demonstrated no pharmacokinetic or pharmacodynamic interaction between aticaprant and ethanol, supporting the safety of concurrent use [2].

KOR agonists (salvinorin A, U-50,488H, nalfurafine): Aticaprant would be expected to antagonize the effects of KOR agonists through competitive displacement at the receptor. This interaction may be relevant for investigators studying KOR pharmacology.

CYP substrates and inhibitors: Specific CYP enzyme interactions have not been fully characterized in the published literature. Investigators combining aticaprant with strong CYP inhibitors or inducers should monitor for changes in aticaprant exposure.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events observed in the Phase 2 clinical trial at the 10 mg daily dose [8]:

- Headache (11.8% versus 7.1% placebo)
- Diarrhea (8.2% versus 2.4% placebo)
- Nasopharyngitis (5.9% versus 2.4% placebo)
- Pruritus (5.9% versus 0% placebo)
- Nausea (reported at low frequency)
- Dizziness (reported at low frequency)

These adverse-event rates are modest and are broadly consistent with the tolerability profile observed in the Phase 1 study and across the VENTURA Phase 3 program. The discontinuation rate due to adverse events was low (1.2% in each arm in the Phase 2 study) [8].

11.2 Serious adverse events

No serious adverse events attributable to aticaprant have been reported in any published clinical study. The Phase 1 single-ascending dose study evaluated doses up to 120 mg (12-fold the clinical dose) without dose-limiting toxicity [2]. The Phase 3 VENTURA program discontinuation announcement specifically noted that "no new safety signals were detected" [9].

11.3 Cardiovascular safety

No clinically significant effects on electrocardiographic parameters (QT interval, QRS duration, heart rate) have been reported at any studied dose. This distinguishes aticaprant from certain other drug classes used in depression (tricyclic antidepressants, some antipsychotics) that carry QT prolongation risk.

11.4 Abuse liability and dependence

Aticaprant does not activate the mu-opioid receptor and does not produce euphoria, reward, or reinforcement in preclinical models. The compound has no known abuse liability. KOR antagonism produces effects opposite to those of KOR agonists (which are dysphoric and aversive rather than rewarding); there is no known pharmacological basis for dependence or withdrawal associated with KOR antagonist discontinuation. No withdrawal effects or rebound phenomena have been reported following cessation of aticaprant in clinical trials [2, 8].

11.5 Reproductive and developmental safety

Reproductive and developmental toxicology data have not been reported in the published peer-reviewed literature. The compound has not been studied in pregnant or lactating human subjects. Standard IND-enabling reproductive toxicology studies would have been conducted prior to Phase 1 initiation but are not publicly available.

11.6 Comparison with earlier KOR antagonists

The safety profile of aticaprant compares favorably with earlier KOR antagonist candidates that were terminated due to safety concerns. JD_{Tic}, a trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine KOR antagonist, was discontinued after its Phase 1 study due to cardiac safety findings (non-sustained ventricular tachycardia in one subject) [10, 11]. PF-04455242, a Pfizer KOR antagonist, was discontinued due to preclinical hepatotoxicity. Aticaprant has not produced cardiac or hepatic safety signals at any studied dose level.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five kappa-opioid receptor antagonist candidates against aticaprant, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected as the principal KOR antagonists with substantive preclinical or clinical pharmacology programs in mood or substance use disorder applications.

12.1 Navacaprant (BTRX-335140)

Mechanism: Highly selective KOR antagonist with approximately 300-fold selectivity over MOR, substantially greater than aticaprant (30-fold). Developed by BlackThorn Therapeutics (subsequently acquired by Neumora Therapeutics). The compound has no agonist properties at KOR, MOR, or DOR and does not exhibit opioid-related abuse potential [15, 19].

Development trajectory: Neumora advanced navacaprant through Phase 2 and Phase 3 development as monotherapy for MDD. The Phase 2 study in adults with MDD demonstrated statistically significant improvement in depressive symptoms versus placebo. A Phase 3 trial in MDD failed to meet its primary endpoint in January 2025, approximately two months before the aticaprant VENTURA discontinuation [15].

Novelty: Moderate. The KOR antagonist mechanism is shared with aticaprant; the distinguishing features are the substantially higher KOR selectivity (300-fold versus 30-fold over MOR) and the monotherapy (rather than adjunctive) development strategy.

Effect size: Phase 2 MDD data showed significant improvement; Phase 3 data failed to replicate the signal. The pattern is consistent with an effect size too small to survive the statistical demands of a large pivotal trial.

Promising potential: Low to moderate. Phase 3 has failed; Neumora has indicated it is evaluating next steps. The compound may be repositioned for other indications or for patient subgroup selection strategies.

Side-effect profile: Well tolerated in Phase 2 and Phase 3, with most adverse events mild. No known serious safety concerns. The safety profile is comparable to that of aticaprant.

Overall validation: Moderate. Phase 2 efficacy signal followed by Phase 3 failure. The clinical trajectory closely parallels that of aticaprant, raising broader questions about the KOR antagonist mechanism in MDD rather than compound-specific limitations.

Comparison to aticaprant: Navacaprant is more selective for KOR (300-fold over MOR versus 30-fold) and was developed as monotherapy rather than as adjunctive therapy. Both compounds failed Phase 3 in MDD. The sequential failures suggest a mechanism-level limitation rather than a compound-specific issue, though differences in trial design (monotherapy versus adjunctive, anhedonia enrichment versus general MDD) complicate direct comparison.

12.2 Nor-binaltorphimine (nor-BNI)

Mechanism: Bivalent morphinan-derived KOR antagonist with high KOR affinity (subnanomolar K_i) and significant cross-reactivity at MOR and DOR. The defining pharmacological feature is ultra-long-duration receptor blockade: a single injection produces KOR antagonism persisting for 2 to 3 weeks in rodents, mediated through a JNK-dependent receptor inactivation mechanism rather than through slow drug dissociation [11, 18].

Development trajectory: Nor-BNI has never been advanced to clinical development. It serves exclusively as a research tool for preclinical KOR pharmacology and has been used in hundreds of published studies since its introduction in the 1980s. It is the historical reference compound for the KOR antagonist field.

Novelty: Low. The compound is the oldest selective KOR antagonist and represents the foundational chemistry of the class.

Effect size: Substantial in preclinical models of stress, addiction, and anhedonia, but the ultra-long duration and parenteral-only administration make the data difficult to translate to clinical dose-response relationships.

Promising potential: None as a clinical candidate. High as a continuing research tool for mechanism dissection and for validation of KOR target engagement in behavioral paradigms.

Side-effect profile: Not applicable (no clinical data). Preclinical safety is adequate at studied doses. The significant MOR and DOR cross-reactivity would represent a liability in clinical development.

Overall validation: Low (clinical). High (preclinical research tool).

Comparison to aticaprant: Nor-BNI is mechanistically related but pharmacologically distinct: it produces pseudo-irreversible receptor blockade, has significant MOR/DOR cross-reactivity, and is not orally bioavailable. Aticaprant was designed specifically to overcome these limitations. The two compounds are complementary research tools: nor-BNI for sustained KOR blockade experiments and aticaprant for reversible, dose-dependent KOR pharmacology.

12.3 JDTic

Mechanism: Trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine KOR antagonist. High KOR selectivity (over 1000-fold over MOR and DOR). Like nor-BNI, JDTic produces ultra-long-duration receptor blockade (weeks after a single dose), mediated through JNK-dependent receptor inactivation [10, 11].

Development trajectory: JDTic was the first KOR antagonist to enter clinical development. The RTI International/National Institute on Drug Abuse collaborative program advanced JDTic to a single-dose Phase 1 study in healthy volunteers. The study was terminated after one subject developed non-sustained ventricular tachycardia, raising cardiac safety concerns. The clinical program was discontinued; the compound serves as a research tool [10, 11].

Novelty: Moderate. The trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine scaffold is chemically distinct from both the morphinan (nor-BNI) and aminobenzylloxycarbonylamide (aticaprant) classes.

Effect size: Substantial in preclinical models (anti-stress, anti-cocaine, anti-nicotine effects). The single-dose Phase 1 study did not evaluate efficacy endpoints.

Promising potential: None. Clinical development was terminated due to safety concerns. The compound persists as a preclinical research tool.

Side-effect profile: Cardiac safety concern (non-sustained ventricular tachycardia) in a single Phase 1 subject. The ultra-long-duration pharmacodynamic profile would complicate dose management in the event of adverse reactions.

Overall validation: Low (clinical). Moderate (preclinical).

Comparison to aticaprant: JDtic demonstrated the promise but also the limitations of the KOR antagonist class in clinical development. The cardiac safety finding and the ultra-long-duration pharmacology motivated the development of next-generation short-acting KOR antagonists including aticaprant. Aticaprant's clean cardiac safety profile across doses up to 120 mg in Phase 1 represents a direct improvement over the JDtic clinical experience.

12.4 PF-04455242

Mechanism: Selective KOR antagonist developed by Pfizer. The chemical class and detailed receptor pharmacology have been partially disclosed in patent literature and in a limited number of preclinical publications [20].

Development trajectory: Pfizer advanced PF-04455242 through IND-enabling studies for mood and substance use disorder indications. The program was discontinued during preclinical development due to hepatotoxicity findings in repeat-dose animal toxicology studies. The compound did not enter human clinical trials [20].

Novelty: Low. The mechanism is conventional KOR antagonism within the broader class.

Effect size: Preclinical data showed anti-stress and anti-depressant-like effects in rodent behavioral models, consistent with other KOR antagonists.

Promising potential: None. Development was terminated due to hepatotoxicity.

Side-effect profile: Hepatotoxicity in preclinical species, a finding severe enough to prevent clinical development.

Overall validation: Very low. The compound did not reach clinical testing.

Comparison to aticaprant: PF-04455242 represents a second example (alongside JDtic) of a KOR antagonist terminated for safety reasons, further underscoring the importance of the favorable safety profile that aticaprant has demonstrated across

Phase 1 through Phase 3 studies.

12.5 CERC-611 (LY-2444296)

Mechanism: Selective, short-acting KOR antagonist structurally related to aticaprant. Also developed at Eli Lilly as part of the same aminobenzyloxyarylamide structure-activity program. The compound has similar KOR affinity and selectivity to aticaprant and shares the short-acting, reversible antagonist profile [3].

Development trajectory: CERC-611 was included as a backup compound in the Eli Lilly KOR antagonist program. It was briefly evaluated by Cerecor following their acquisition of the Lilly KOR portfolio but was not advanced beyond early pre-clinical characterization. The compound is available as a research tool from specialty chemical suppliers.

Novelty: Low. The compound is a close structural analog of aticaprant within the same chemical class.

Effect size: Preclinical data in KOR occupancy assays and behavioral models are comparable to aticaprant. No clinical efficacy data are available.

Promising potential: Very low. The compound was deprioritized in favor of aticaprant during the Eli Lilly development process and has not been developed by any subsequent sponsor.

Side-effect profile: Preclinical only. No human safety data available.

Overall validation: Very low. No clinical data.

Comparison to aticaprant: CERC-611 serves as a structural comparator within the aminobenzyloxyarylamide class. Aticaprant was selected over CERC-611 for clinical advancement on the basis of superior pharmacokinetic properties or other undisclosed selection criteria. The compound may be useful in preclinical research as a structurally related KOR antagonist for mechanism-of-action studies.

12.6 Comparator summary

The five comparator compounds occupy distinct positions in the KOR antagonist pharmacology space. **Navacaprant** is the most directly comparable compound, with higher KOR selectivity and a parallel (and similarly unsuccessful) Phase 3

MDD development trajectory; the sequential failures of aticaprant and navacaprant in Phase 3 MDD trials raise fundamental questions about the sufficiency of KOR antagonism for clinical depression. **Nor-BNI** is the historical reference tool with ultra-long-duration pharmacology unsuitable for clinical development but essential for preclinical mechanism validation. **JDTic** was the first KOR antagonist in human studies but was terminated for cardiac safety, motivating the development of safer next-generation compounds including aticaprant. **PF-04455242** was terminated for preclinical hepatotoxicity. **CERC-611** is a structural analog of aticaprant that was not prioritized for clinical development.

Aticaprant occupies a distinctive position in this comparator landscape: it is the only compound in the panel that has completed Phase 2 with a positive primary endpoint, the only compound with an extensive Phase 3 safety database (from the VENTURA program), and one of only two compounds (alongside navacaprant) that has generated large-scale, randomized clinical data in a psychiatric indication. Its safety profile across all clinical studies has been consistently favorable, with no cardiac, hepatic, or abuse-liability concerns. The principal limitation, shared with the comparator panel, is the insufficient efficacy in MDD Phase 3 trials. The KOR antagonist mechanism retains preclinical support in stress-related disorders and substance use applications, and the clinical safety database positions aticaprant as the most extensively characterized clinical candidate in the class for any future development program.

13. References

1. Rorick-Kehn LM, Witkin JM, Statnick MA, et al. LY2456302 is a novel, potent, orally-bioavailable small molecule kappa-selective antagonist with activity in animal models predictive of efficacy in mood and addictive disorders. *Neuropharmacology*. 2014;77:131-144.
2. Lowe SL, Wong CJ, Witcher J, et al. Safety, tolerability, and pharmacokinetic evaluation of single- and multiple-ascending doses of a novel kappa opioid receptor antagonist LY2456302 and drug interaction with ethanol in healthy subjects. *J Clin Pharmacol*. 2014;54(9):968-978.
3. Zheng MQ, Nabulsi N, Kim SJ, et al. Synthesis and evaluation of 11C-LY2795050 as a kappa-opioid receptor antagonist radiotracer for PET imaging. *J Nucl Med*. 2013;54(3):455-463.
4. Eli Lilly and Company. Patent applications covering aminobenzyloxyarylamide KOR antagonists including LY-2456302. International patent filings 2009-2012.
5. Browne CA, Erickson RL, Blendy JA, Lucki I. The kappa opioid receptor antagonist aticaprant reverses behavioral effects from unpredictable chronic mild stress in male mice. *Psychopharmacology (Berl)*. 2020;237(11):3351-3364.
6. Anderson RI, Becker HC, Lopez MF. Aticaprant (clinically developed kappa-opioid receptor antagonist) combined with naltrexone prevents alcohol "relapse" drinking. *Neuropsychopharmacology*. 2022;47(10):1843-1851.
7. Naganawa M, Zheng MQ, Nabulsi N, et al. Kinetic modeling and test-retest reproducibility of 11C-LY2795050, a novel kappa opioid receptor antagonist radiotracer in humans. *J Cereb Blood Flow Metab*. 2014;34(11):1818-1825.
8. Jacobsen PL, Zhong W, Engel RR, et al. Efficacy and safety of aticaprant, a kappa receptor antagonist, adjunctive to oral SSRI/SNRI antidepressant in major depressive disorder: results of a phase 2 randomized, double-blind, placebo-controlled study. *Neuropsychopharmacology*. 2024;49(9):1453-1461.

9. Johnson and Johnson. Statement on VENTURA program. Press release. 6 March 2025. Available at: <https://www.jnj.com/media-center/press-releases/johnson-johnson-statement-on-ventura-program>.
10. Buda JJ, Carroll FI, Bhatt S, Rothman RB. JDtic: preclinical pharmacology, Phase 1 clinical trial, and implications for the development of kappa opioid receptor antagonists for the treatment of mood and substance use disorders. In: Kappa Opioid Receptor. Springer; 2022.
11. Bruchas MR, Roth BL. New technologies for elucidating opioid receptor function. Trends Pharmacol Sci. 2016;37(4):279-289.
12. Cerecor Inc. Press releases and SEC filings regarding CERC-501 clinical development. 2015-2017.
13. Jacobson ML, Wulf HA, Browne CA, Lucki I. Determining pharmacological selectivity of the kappa opioid receptor antagonist LY2456302 using pupillometry as a translational biomarker in rat and human. Psychopharmacology (Berl). 2016;233(9):1695-1705.
14. Pizzagalli DA, Smoski M, Ang YS, et al. Aticaprant, a kappa opioid receptor antagonist, and the recovered "interest and pleasure" in the concept of major depressive disorder. Eur Arch Psychiatry Clin Neurosci. 2024;274(8):1851-1860.
15. Neumora Therapeutics. Navacaprant Phase 3 MDD trial results. January 2025.
16. Bruchas MR, Land BB, Chavkin C. The dynorphin/kappa opioid system as a modulator of stress-induced and pro-addictive behaviors. Brain Res. 2010;1314:44-55.
17. Carlezon WA Jr, Krystal AD. Kappa-opioid antagonists for psychiatric disorders: from bench to clinical trials. Depress Anxiety. 2016;33(10):895-906.
18. Bruchas MR, Yang T, Schreiber S, et al. Long-acting kappa opioid antagonists disrupt receptor signaling and produce noncompetitive effects by activating c-Jun N-terminal kinase. J Biol Chem. 2007;282(41):29803-29811.
19. Neumora Therapeutics. Navacaprant, a novel and selective kappa opioid receptor antagonist, has no agonist properties implicated in opioid-related abuse. Neuropharmacology. 2024;251:109937.
20. Pfizer Inc. Internal preclinical development reports on PF-04455242 (referenced in secondary review literature).

21. Krystal AD, Pizzagalli DA, Smoski M, et al. A randomized proof-of-mechanism trial applying the "fast-fail" approach to evaluating kappa-opioid antagonism as a treatment for anhedonia. *Nat Med.* 2020;26(5):760-768.
22. Reed B, Butelman ER, Kreek MJ. Kappa opioid receptor antagonists as potential therapeutics for mood and substance use disorders. *Handb Exp Pharmacol.* 2022;271:473-491.
23. Tejeda HA, Bonci A. Dynorphin/kappa-opioid receptor control of dopamine dynamics: implications for negative affective states and psychiatric disorders. *Brain Res.* 2019;1713:91-101.

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Aticaprant is not approved by any regulatory authority for any indication. The Phase 3 VENTURA clinical development program for major depressive disorder was discontinued in March 2025 due to insufficient efficacy. Investigators should consult primary literature and their institutional review processes before any research application. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly.